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Clinical and psychological factors associated with nebuliser adherence among adults with cystic fibrosis

By:

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A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy

The University of Sheffield
Faculty of Medicine, Dentistry and Health
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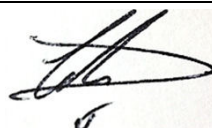
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ABSTRACT

Background:

Daily nebuliser use is crucial for people with cystic fibrosis (CF) to stay healthy, but average adherence is only 35-50%. Making nebuliser use 'habitual' (i.e. automatic) may aid adherence, but extant CF literature has mainly focused on treatment burden and factors involving conscious deliberation. This thesis aims to explore a broad range of clinical and psychological factors that are potentially associated with objective nebuliser adherence among adults with CF.

Methods:

This thesis encompassed three studies. First, a retrospective analysis of adherence data captured using chipped nebulisers from 2013-2016 among 126 adults was performed to explore relevant clinical factors. Second, a mixed-methods study was performed among 20 adults to identify the psychological factors differentiating high or low nebuliser adherence patterns (i.e. $\geq 80\%$ or $< 50\%$ of all nebulised treatments over one year). Third, a secondary quantitative analysis was performed using data from a two-centre pilot adherence trial among 64 adults to replicate findings from the mixed-methods study.

Results:

The retrospective analysis showed a U-shape relationship between adherence and age, with lowest adherence levels among adults aged 19-25 years. Lower adherence was also noted for long term (> 3 months) nebuliser regimen in comparison to shorter-term treatments.

The mixed-methods study found stronger habit and greater opportunities among high adherers, though habit and perceived opportunity scores were highly positive correlated. Habit attenuated the relationship between treatment complexity and perceived treatment burden. Indeed, in interviews, high adherers reported that routinisation and greater automaticity made treatment burden more manageable.

The secondary analysis using pilot trial data found stronger habit and lower concerns among high adherers. In an ordinal regression model, only habit strength was independently associated with adherence.

Conclusion:

Adherence to long-term CF nebuliser treatments is problematic, especially among younger adults with CF. Habit may attenuate perceived burden and is a promising target for adherence interventions.

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LIST OF JOURNAL PUBLICATIONS DIRECTLY RELATED TO THE THESIS

1. **Hoo ZH**, Boote J, Wildman MJ, Campbell MJ, Gardner B. Determinants of objective adherence to nebulised medications among adults with cystic fibrosis: an exploratory mixed methods study comparing low and high adherers. *Health Psychol Behav Med* 2017;5:299-316.

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2. **Hoo ZH**, Gardner B, Arden MA, Waterhouse S, Walters SJ, Campbell MJ, Hind D, Maguire C Dewar J, Wildman MJ. Role of habit in treatment adherence among adults with cystic fibrosis. *Thorax* 2018 Jun 9 [Epub ahead of print]

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LIST OF CONFERENCE PRESENTATIONS / AWARDS DIRECTLY RELATED TO THE THESIS

Oral presentations:

1. European Health Psychology Society and British Psychological Society Division of Health Psychology Conference, Aberdeen, 2016
 - a. Determinants of objective adherence to nebulised medications among adults with CF

Poster presentations:

1. European CF Society Conference, Seville, 2017
 - a. Demographic and treatment factors associated with objective nebuliser adherence among adults with CF

OTHER JOURNAL PUBLICATIONS RELATED TO THE PhD RESEARCH

1. **Hoo ZH**, Curley R, Campbell MJ, Walters SJ, Hind, D, Wildman MJ. Accurate reporting of adherence to inhaled therapies in adults with cystic fibrosis: methods to calculate “normative adherence”. *Patient Prefer Adherence* 2016;10:887-900.

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2. **Hoo ZH**, Campbell MJ, Curley R, Wildman MJ. An empirical method to cluster objective nebulizer adherence data among adults with cystic fibrosis. *Patient Prefer Adherence* 2017;11:631-42.

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3. **Hoo ZH**, Wildman MJ, Curley R, Walters SJ, Campbell MJ. Rescue therapy within the UK Cystic Fibrosis Registry: An exploration of predictors of intravenous antibiotic use amongst adults with CF. *Respirology* 2018;23:190-7.

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4. **Hoo ZH**, Campbell MJ, Curley R, Walters SJ, Wildman MJ. Do cystic fibrosis centres with the lowest FEV₁ still use the least amount of intravenous antibiotics? A registry-based comparison of intravenous antibiotic use among adult CF centres in the UK. *J Cyst Fibros* 2018;17:360-7.

Contribution statement: Together with MJW, I was the originator of the idea for this registry analysis. I was responsible for study design, data request (from the UK CF registry), analysis and interpretation. I drafted the manuscript, and managed the review & publication process. I am the corresponding author for this manuscript.

5. **Hoo ZH**, Edenborough FP, Curley R, Prtak L, Dewar J, Allenby MI, Nightingale JA, Wildman MJ. Understanding *Pseudomonas* status among adults with cystic fibrosis: a real-world comparison of the Leeds criteria against clinicians' decision. *Eur J Clin Microbiol Infect Dis* 2018;37:735-43.

Contribution statement: I was the originator of the idea for this study. I was responsible for study design, data collection, analysis and interpretation. I drafted the manuscript, and managed the review & publication process. I am the corresponding author for this manuscript.

6. **Hoo ZH**, Coates E, Maguire C, Cantrill H, Shafi N, Nash EF, McGowan A, Bourke SJ, Flight WG, Daniels TV, Nightingale JA, Allenby MI, Curley R, Wildman MJ. Pragmatic criteria to define chronic *Pseudomonas aeruginosa* infection among adults with cystic fibrosis. *Eur J Clin Microbiol Infect Dis* 2018 Aug 3 [Epub ahead of print]

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7. **Hoo ZH**, Curley R, Campbell MJ, Walters SJ, Wildman MJ. The importance of data issues when comparing cystic fibrosis registry outcomes between countries: Are annual review FEV1 in the UK only collected when subjects are well? *J Eval Clin Pract* 2018;24:745-51.

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OTHER CONFERENCE PRESENTATIONS / AWARDS RELATED TO THE PhD RESEARCH

Oral presentations:

1. European CF Society Conference, Basel, 2016
 - a. Predictors of intravenous antibiotic use among adults with CF
2. European CF Society Conference, Seville, 2017
 - a. Do CF centres with the best FEV₁ still use the most rescue therapy?

Poster presentations:

1. British Thoracic Society Winter Meeting, London, 2015
 - a. Changes in adherence and health outcomes among adults with CF in Sheffield from 2013 to 2014
2. European CF Society Conference, Basel, 2016
 - a. Impact of nebuliser adherence on subsequent rescue therapy with IV antibiotics among adults with CF §

§ This was awarded the 'Best ECFS Poster Award' for epidemiology / registry category.

3. North American CF Conference, Orlando, 2016
 - a. Differences in 'unadjusted adherence' vs 'normative adherence'
 - b. The importance of data completeness to determine centre-level nebuliser adherence levels
4. European CF Society Conference, Seville, 2017
 - a. Inter-rater reliability and face validity of clinicians' consensus decision for *P. aeruginosa* status among adults with CF
 - b. Comparison of the Leeds criteria vs clinicians' consensus for *P. aeruginosa* status
 - c. Using the Leeds criteria and clinicians' decision to determine *P. aeruginosa* status among participants of the ACtiF pilot study
 - d. Cluster analysis of objective nebuliser adherence data among adults with CF
5. North American CF Conference, Indianapolis, 2017
 - a. Real world evidence of sustained improvement in objective adherence to preventative inhaled therapies in an adult CF centre
 - b. Exploring different methods to display centre-level data in the UK CF Registry annual report
 - c. Are UK annual review FEV₁ readings only collected when subjects are well?
 - d. Does bias in annual review FEV₁ affect between-centre comparison within the UK?

CHAPTER 1: INTRODUCTION TO THE THESIS

Cystic fibrosis (CF) is a long-term condition in which median survival is around 45-50 years.[1] More than 80% of the mortality is primarily due to lung disease,[2] and daily use of preventative inhaled therapies is crucial to maintain lung health.[3] However, adherence to these therapies among adults with CF is generally low with median adherence of 35-50%.[4, 5]

Nebuliser adherence among adults with CF remains poorly understood. Most of the current literature in this area tends not to emphasise explicit psychological behaviour change theory; and tends to focus on treatment burden and conscious motivational factors such as treatment beliefs.[6] Within the wider psychology literature, there is increasing recognition of the importance of automatic, non-reflective processes to improve and sustain treatment adherence.[7-11] One such automatic process is habit. While used in everyday language to refer to frequent repetitive actions, within psychology the term 'habit' refers to a non-conscious process by which situational cues (e.g. watching the BBC News at Ten) automatically prompt an impulse to perform an action (e.g. using nebuliser).

It should be noted that low adherence is not a recent phenomenon in CF. Medication adherence has been recognised as a challenge in managing people with CF since 1970's,[12] just as efficacious CF treatment options began to emerge. Research to develop adherence interventions for people with CF has begun in earnest during 1980's,[13] yet today there are no effective interventions to support adherence in routine clinical practice.[14, 15] Indeed, a substantial amount of background work is required before such an intervention can be successfully developed and implemented. This PhD research was undertaken to explore various issues related to the development, evaluation and implementation of effective adherence interventions for adults with CF.

The work presented in this thesis was undertaken with the specific aims of exploring a broad range of clinical and psychological factors that are potentially associated with objective nebuliser adherence among adults with CF; since understanding the determinants of adherence is an important step towards designing an effective adherence intervention. The remainder of this thesis is structured into the following chapters.

Chapter 2 provides a brief introduction to cystic fibrosis; and describes changes in epidemiology, prognosis and treatment options over the past few decades.

Chapter 3 reviews the current literature pertaining to clinical and psychological factors that are associated with nebuliser adherence among people with CF. Since no studies specifically looked at habit in the context of CF medication adherence, the role of 'habit' in other health-related behaviours was also summarised.

Chapter 4 seeks to address the following research question: What are the clinical factors associated with objective adherence? In this chapter, routinely collected data from 2013-2016 among 126 adults with CF were analysed to explore the clinical (i.e. demographic and treatment) factors that are associated with objective nebuliser adherence.

Chapter 5 seeks to address the following research question: What are the psychological factors associated with objective adherence? This chapter reports the findings of a mixed methods cross-sectional exploratory study comparing ten low and ten high nebuliser adherers. The results from this chapter have been recently published.[16]

Chapter 6 seeks to replicate the findings of the Sheffield mixed methods study in Chapter 5. This chapter reports the findings of a secondary quantitative analysis using prospectively collected data during a pilot randomised controlled trial with 64 participants (ACtiF pilot, ISRCTN13076797). The results from this chapter have been recently published.[17]

The final chapter (Chapter 7) ends with discussion and conclusions that draw together the findings from previous chapters.

CHAPTER 2: INTRODUCTION TO CYSTIC FIBROSIS

This chapter summarises the relevant literature to set the scene and to provide a background on the management of cystic fibrosis (CF).

Chapter 2, Section 1: What is cystic fibrosis?

Cystic fibrosis (CF) is an autosomal recessive genetic condition that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[18] More than 1500 mutations have been identified in the CFTR gene, with F508del accounting for almost 2/3 of these mutations.[19] The CFTR gene encodes the CFTR protein, which is expressed in the apical membrane of epithelial cells and predominantly functions as a chloride channel.[20, 21] CFTR also has other roles, including regulating sodium and bicarbonate transport.[18] CFTR is found throughout the body; hence CF is a multi-system condition.[18] However, the two organs that are mainly affected are lungs (resulting in recurrent infections and respiratory failure) and the gastrointestinal tract (resulting in malabsorption and poor growth).[20] At present, more than 80% of the mortality in CF is primarily due to lung disease;[2, 20] hence the most important aims of CF treatments are to try protect the lungs from the recurrent infections, inflammation and permanent lung damage that are the hallmarks of CF lung disease.[22]

There are two theories for the pathogenesis of CF lung disease from CFTR dysfunction. The 'low volume' hypothesis postulates that excess sodium and water reabsorption result in reduced volume of airway surface liquid, which then inhibits mucociliary clearance and leads to mucus plugging.[20, 21, 23] The 'high salt' hypothesis postulates that retained excess sodium and chloride in airway surface liquid disrupts the innate defence mechanism.[21, 24] CF lungs are therefore more vulnerable to infection and colonisation by pathogens. There is also disproportionately exuberant neutrophil-dominated inflammatory response to the pathogens due to dysregulated host inflammatory response.[20-22, 24] This vicious cycle of infection and inflammation then leads to progressive worsening of lung damage (e.g. bronchiectasis), respiratory failure and death.[18, 20]

Given the extensive number of CFTR gene mutations that can cause CF, it is not surprising that there is a wide spectrum of disease severity.[25-27] The CFTR gene mutations are divided into five functional classes based on the different molecular defects of the CFTR proteins.[19] People who are homozygous for Class I-III mutations tend to have more severe disease than those with at least a copy of the Class IV-V mutation.[19, 28] However, there is substantial phenotypic variability even among people with identical CF genotype, due to presence of unlinked 'modifier genes' and also environmental influences.[28-32] The latest evidence shows that people with 'milder phenotype' tend to eventually succumb to the same trajectory of lung function decline experienced by people

with 'typical CF'; suggesting that progressive lung damage is only delayed rather than completely avoided among people who may appear to have milder forms of CF.[33]

Chapter 2, Section 2: Changes in the prognosis and epidemiology of people with CF

The median survival was less than 6 months when CF was first recognised as a unique entity in 1938.[34] Survival improved from the 1950's, as people with CF began to be cared for in 'specialist centres'.[34] As clinicians gained more experience, treatment options increased and quality of care improved, survival continued to improve year on year; and median survival in CF is now estimated to be around 45-50 years.[35-37] It is important to note that the survival improvement among people with CF outstrips the background survival improvement among the general population [38] and the improvement is not simply due to the increased case finding of people with milder disease.[39]

The improvement in prognosis has altered the demography of the CF population.[40, 41] Up to the 1970's, CF was predominantly a disease of children.[42, 43] From 2010, the number of adults has actually exceeded the number of children with CF in many developed countries.[36, 41, 44] The most recent (2016) UK CF registry report described a population of more than 10,000 affected people,[1] making CF the most common genetic life-shortening long-term condition in the UK.[20, 21] More than 50% of the people with CF in the UK are aged ≥ 16 years, hence receiving care at specialist adult centres. The adult CF population continues to increase at more than 200 people per year,[39] which is equivalent to size of a moderately large adult CF centre. With the adult CF population projected to increase by 30-40% in the next 10 years, there will be increasing pressure on the current adult CF services.[35, 40] Therefore, there is a need to explore new care models in order to accommodate increased patient numbers without any reduction in the quality of care.

Chapter 2, Section 3: The 'three pillars' of CF management

Treatment regimen for a person with CF typically consists of multiple components due to the multi-system nature of CF. In general, CF management can be summarised into the following 'three pillars':[34, 45]

- Nutritional supplementation with appropriate pancreatic enzyme replacement, high calorie diet, nutritional supplement (including replacement of fat-soluble vitamins) and appropriate management of CF related diabetes
- Airway clearance with inhaled mucolytics (including osmotics) and chest physiotherapy
- Appropriate use of antibiotics to eradicate / control airway infection – antibiotics can be delivered in three different routes i.e. intravenous (IV), oral or inhaled

Optimal CF management is proactive. Early interventions should be initiated prior to the development of symptoms [34, 45] because lung damage can occur prior to the onset of any symptoms, as demonstrated by CT scans or lung clearance index in infants with CF.[46-48]

Recent research hints at the possibility of eventual cure with new treatments targeting the underlying gene defect.[49-51] However, only around 5% of the UK CF population (those with the class III gene mutation) currently benefits from ivacaftor, a 'CFTR potentiator' that has been commercially available since 2012-2013.[52] The rest of the CF population still rely on treatments that target the downstream consequences of CFTR dysfunction in the lungs i.e. the impaired mucociliary clearance and chronic infection / inflammation. The impressive improvement in CF survival over the past 30-40 years emphasises the potency and efficacy of these 'downstream treatments'.

Chapter 2, Section 4: 'Rescue' vs 'preventative' therapies in CF

Treatments to preserve lung health in CF can be broadly dichotomised into '*rescue*' therapy with IV antibiotics to *treat* pulmonary exacerbations and '*preventative*' therapy with inhaled therapies to *minimise the risk* of exacerbations.[53] "Pulmonary exacerbations" are episodic acute events causing damage to the lung, usually precipitated by infection and manifest as acute worsening of symptoms and/or drop in lung function (FEV₁).[54-56] Frequent exacerbations are associated with excess mortality,[57, 58] accelerated FEV₁ decline,[59-63] lower quality of life,[64-67] and higher healthcare costs.[68-70] Therefore, these are events with clinically significant consequences for a person with CF. In fact, it has been postulated that recurrent pulmonary exacerbations is the primary driver of progressive lung damage seen in people with CF.[71, 72]

The use of IV antibiotics as acute treatments for exacerbations actually have very limited RCT evidence.[73] Nonetheless, various observational studies have highlighted the importance of IV antibiotics in CF. A recent analysis using the Epidemiologic Study of Cystic Fibrosis (ESCF) data showed that treatment of exacerbations with any additional antibiotics is associated with increased likelihood of FEV₁ recovery, when compared with no treatment.[74] Recent studies using the US CF Foundation Patient Registry and ESCF data have suggested that the best outcomes (i.e. increased likelihood of FEV₁ recovery and reduced risk of treatment failure) are achieved with IV antibiotics (especially in-patient IV courses) compared to additional antibiotics delivered by other routes.[74-76] There is also evidence that inadequate IV antibiotics use or higher threshold for initiating IV antibiotics in the face of an exacerbation is associated worse outcomes,[77, 78] even in this decade when efficacious preventative therapies are increasingly available and increasingly prescribed.[79] As such, IV antibiotic is widely considered to be the most potent treatment for exacerbations,[34] and is recommended by all major CF guidelines to treat exacerbations.[80-83]

Despite the importance of IV antibiotics in CF management, intensive IV use is not without its drawbacks. The common problems associated with widespread antibiotics use in the general population are different from specific problems encountered by people with CF. For example, one of the most common and feared complications of prolonged broad spectrum antibiotics use in the general population is *Clostridium difficile* colitis.[84, 85] *Clostridium difficile* colitis is surprisingly rare among people with CF despite the industrial quantities of IV antibiotics used.[86, 87] Antibiotic resistance is another well-publicised and much-hyped risk with “antibiotics overuse” in the general population.[88-90] Antibiotic resistance is also a problem in CF,[91, 92] but there are several lung pathogens in CF such as *P. aeruginosa* whereby resistance can result from antibiotics under-use e.g. the use of a single IV antibiotic agent (instead of two antibiotics from different classes) can exert selective pressure for resistance to develop.[93-95]

The specific problems due to wide-spread broad-spectrum IV antibiotic use faced by people with CF are just as serious. Hypersensitivity reactions to IV antibiotics are around thrice as common among the CF population.[96-99] Even without a full-blown anaphylaxis, other systemic side-effects such as ototoxicity, malaise, nausea / vomiting or even candidiasis can be debilitating and contribute to the lower quality of life that people with CF experienced during pulmonary exacerbations.[65, 97, 100-102] But perhaps the most catastrophic complication of excessive IV antibiotics use in CF is renal failure. *P. aeruginosa*, which is the most common lung pathogen causing accelerated FEV₁ decline among adults with CF,[62, 103-105] is particularly resistant and two common classes of anti-Pseudomonal antibiotics (aminoglycoside and polymixin) are nephrotoxic.[106] As survival of the CF population improves (see Section 2.2), the cumulative burden of these nephrotoxic antibiotics also increases. Not surprisingly, renal failure is an increasingly a common problem among people with CF.[107-110] In addition to the usual morbidities associated with renal problems, renal failure is particularly pertinent for people with CF because it can limit the use of IV antibiotics and preclude consideration for lung transplantation,[111] both of which are vital treatments to improve prognosis in CF.[34, 112]

Current strategies to limit this “epidemic” of acute renal failure include using aminoglycoside with the least nephrotoxic profile (e.g. tobramycin instead of gentamicin)[113] and to use less toxic dosing regimen (e.g. once daily instead of thrice daily dosing for aminoglycoside).[114] A more sensible approach to limit the systemic side-effects of IV antibiotics would be to move from ‘rescue’ to ‘prevention’,[53] i.e. to use preventative inhaled therapies more effectively with the aim of achieving stability in lung health and reducing the reliance on rescue by IV antibiotics

Unlike IV antibiotics, the efficacy of preventative inhaled therapies has been repeatedly and consistently demonstrated in RCT settings. Multiple blinded randomised control trials found that inhaled therapies reduce the frequency of exacerbations and improve FEV₁. [115-119] In addition, inhaled therapies are associated with improved quality of life and better survival.[120-122] Inhaled

therapies are also recommended in all the major CF guidelines on the basis of their beneficial effects in preserving lung health and reducing the risk of exacerbations.[80, 123, 124]

Preventative treatments can be divided into two categories: antibiotics and mucolytics. Inhaled antibiotics such as colistin, tobramycin, aztreonam lysine and levofloxacin are used in CF to eradicate *P. aeruginosa* when it is first isolated and to prevent pulmonary exacerbations among those who are chronically infected with lung pathogens such as *P. aeruginosa*. [115, 125] These antibiotics are available as solution for nebulisation, or as dry powder for inhalation (colistin and tobramycin only). [126] Inhaled mucolytics are used to aid mucociliary clearance of mucus and augment airway clearance. [127] Mucolytics are also available in the form of solution for nebulisation (e.g. dornase alfa and hypertonic saline) and dry powder for inhalation (e.g. mannitol). [127]

Inhaled therapies have several advantages over other methods of administering medications to the lungs of people with CF. It is possible to achieve much higher intrapulmonary drug concentrations using the inhaled route compared to using systemic routes, such as IV administration. [125, 128, 129] This is of particular importance with the administration of antibiotics, because intrapulmonary concentrations far exceeding the minimum inhibitory concentrations can be achieved with the inhaled route, thus potentially overcoming problems of antibiotic resistance. [130, 131] Crucially, there is minimal systemic absorption of drugs delivered by the inhaled route, thus systemic side-effects are rare. [125, 128, 130, 132, 133] Whilst “local” side-effects such as laryngeal irritation or bronchospasm may occur, [127, 134] these side-effects are usually transient and can be overcome by pre-treatment with bronchodilator or switching to another drug. [135]

Chapter 2, Section 5: The current state of preventative inhaled therapy prescription by CF clinicians

A move from ‘rescue’ to ‘prevention’ would be expected to improve the quality of life and overall health outcomes for people with CF. [53] However, a potential obstacle to this move is the ineffectual utilisation of preventative inhaled therapies despite their proven track record of efficacy.

In clinical medicine, there is always a lag in translating sound evidence into routine practice. Compelling evidence for using aspirin as secondary prophylaxis following acute myocardial infarction emerged around 1970’s and 1980’s, [136-139] yet more than 50% of patients did not receive aspirin on discharge following a myocardial infarction in the 1990’s. [140-142] Another example is the failure to embed hand-washing into current routine clinical practice [143] despite strong evidence for hand-washing emerging since 1846. [144]

In CF, various quality improvement initiatives have increased the appropriate prescription of inhaled treatments. During the mid-1990’s, only around 60% of the eligible people with CF at the

Northern New England CF collaboration (NNECF) were prescribed with inhaled antibiotic and mucolytic.[145] By 2000, the prescription rate has improved to 82% of the eligible people with CF.[145] The prescription of inhaled therapies continued to rise between 1995 and 2005, when no new classes of antibiotics or mucolytics were introduced.[146] With the introduction of a third class of inhaled antibiotics, not surprisingly prescription of inhaled antibiotics increased further and more people are now on multiple classes of inhaled antibiotics (usually being rotated rather than being used simultaneously).[147] In fact, a recent RCT aiming to randomise participants to continuous alternating therapy vs intermittent treatment regimen failed to recruit adequate number of participants, because the number of potentially eligible participants was reduced by the widespread adoption of continuous alternating therapy in the US.[148]

However, there remains substantial variation in the prescription of inhaled therapies.[149-151] Recent data from the US suggest only around two-thirds of people with CF were prescribed the recommended preventative inhaled therapies.[149, 152] In the UK, the most recent CF registry report in 2016 showed an almost 3-fold difference (86.8% vs 30.2%) in the prescription of dornase alfa between the adult CF centre in the UK with the highest dornase alfa use compared to the centre with the lowest use.[1] This difference is simply too large to be explained by just case-mix and chance, and must be due to differences in prescribing practices of CF clinicians.

Appropriate prescription by clinicians is only one side of the coin for effective utilisation of preventative inhaled therapies in CF to enable the move from 'rescue' to 'prevention'. [153, 154] The other side of the coin is medication adherence. Medication adherence, which is the focus of this thesis, is the subject of literature reviews in the next chapter (Chapter 3).

CHAPTER 3: LITERATURE REVIEW

Chapter 3, Section 1: Introduction

3.1.1 The definition of medication adherence

Medication adherence is defined by the World Health Organisation (WHO) as “the degree to which a person’s behaviour corresponds with the agreed recommendations from a health care provider”.[155] The Ascertaining Barriers to Compliance (ABC) taxonomy for medication adherence outlined three distinct temporal adherence phases.[156-158] The first phase is ‘initiation’, which is the period between medication being prescribed and the first dose being taken. ‘Initiation’ is often operationalised as a binary event, whether a patient starts taking the medication or not within a given time period. The second phase is ‘implementation’, which measures the extent to which medication taking corresponds to an agreed dosing regimen from initiation until the final dose. The third phase is ‘persistence’, which is the time between ‘initiation’ and eventual treatment discontinuation.

Most adults with CF would have already received their first dose of inhaled medication during their childhood. Among the minority who were diagnosed with CF in adulthood, their first dose of inhaled medication would still be given in hospital as all CF inhaled therapies require a supervised test dose. Persistence is difficult to operationalise since most adults with CF will remain on inhaled therapies until the end of life, though there may be long periods of non-adherence in between medication doses. Therefore, the ‘implementation’ phase is the most relevant component for medication adherence among adults with CF and is the focus of this thesis.

3.1.2 Methods of capturing adherence data

In general, the two most common methods of capturing adherence data are self-report (i.e. asking respondents to characterise their medication taking behaviour) and pharmacy refill (i.e. measuring how much of the prescribed medications are actually collected).[159, 160] Another method of capturing adherence data is with electronic data capture (EDC), whereby medication taking behaviour is directly monitored via specifically designed electronic devices.

Self-reported measures tend to over-estimate adherence levels, even with validated tools.[4, 161-163] This has resulted in suggestions of using “correction factors” or modelling techniques (e.g. hierarchical linear modelling) to obtain more accurate estimates of adherence levels from self-reported measures.[159, 163, 164] However, these “correction factors” or modelling techniques may not necessarily improve the reliability of self-reported measures because mis-calibration can result in both under- and over-estimation of adherence levels with no clear predictors for the

direction of errors.[4] A significant minority of people under-estimate their adherence,[4] which could potentially result in poor prescribing practices if clinicians were to act upon those self-reported measures. As such, self-reported adherence data are unreliable measures of adherence levels at an individual level.

Pharmacy refill may be somewhat more reliable than self-report, in that it represents the maximum amount of medication a person can take.[165] For example, someone who only collects 20% of his / her prescribed medications can only have a maximum adherence level of 20%, assuming that he / she has no other sources of that medication (e.g. spare supply at home due to previous under-use). However, not all collected medications will be used correctly and some medications may not even be used at all. A study found a mean adherence level of only 62% using EDC among hospitalised children with CF even though prescription charts recorded 100% of inhaled therapies as being administered.[166] If handing over an inhaled medication in a hospital setting (where there is less distraction and more attention is being focused on health) does not equate to the medication actually being used, it seems highly unlikely that all collected medications in the community will be used. That means pharmacy refill may over-estimate adherence. Indeed, a study evaluating adherence with ivacaftor among people with CF found higher adherence levels as measured by pharmacy refill (median 84%) compared to EDC (median 61%).[167] Perhaps even more worrying, there was a lack of correlation between adherence levels measured by those two different methods in that study.[167] Another limitation of pharmacy refill is the inability to capture important granularity of behaviours involved in using preventative inhaled therapies.

EDC is generally regarded as the 'gold standard' method to capture adherence data due to its accuracy.[168] In CF, tamper-proof intelligent nebuliser systems (I-neb®) which provide date- and time-stamped data for every dose of nebulised medication are routinely available.[169] The I-neb® is a third generation adaptive aerosol delivery system designed to optimise inhalation technique by directing flow and depth of inhalation, providing positive feedback signals to guide user, and only delivering aerosol when an inhalation of sufficient quality is detected.[170] By only delivering aerosol during active inhalation, I-neb® also avoids the issue of medication dose dumping, thus ensuring the adherence data are more robust. Another general advantage of EDC is that it provides richer quantitative data compared to other methods of data capture. By logging every episode of medication use, EDC provides a continuous stream of data which allows adherence pattern to be studied in greater detail.[156] For example, weekly ivacaftor adherence rates was found to vary substantially between participants and to decline by a rate of 1.93% per week using EDC.[167] In terms of nebuliser adherence, studies using I-neb® found that adolescents with CF are most adherent during weekdays of school term-time.[171] This has important implications towards understanding the psychological factors that influence adherence and such insight is only possible with the data captured by EDC.

This is not to say that the current methods for EDC have no disadvantages. A specific problem related to nebulisers such as I-neb® is that it is sometimes used to deliver more than one type of medications. In that situation, it is not possible to differentiate which medication was actually being used or not used. A more general problem is that any electronic device may malfunction, thus missing data is a risk.[163] With less robust EDC, medication dose dumping (i.e. medication is removed but not ingested correctly) may occur but not be detected. This is less of a problem with more sophisticated EDC devices that can measure the technique of using the medication.[172, 173] Availability of suitable devices is also an issue – not every treatment modality can be monitored using EDC. In CF, EDC for dry powder inhalers are not yet routinely available. Cost is often cited as another barrier to using EDC.[163] Nonetheless, EDC for nebulised medications in CF is already routinely available.[169] If EDC is used effectively to provide feedback and improve adherence, a health economics evaluation suggests those devices will more than justify their costs.[174]

On balance, the advantages of capturing adherence data using EDC for preventative inhaled therapies in CF do seem to outweigh the disadvantages. Therefore, only adherence data captured via EDC are used for analysis for the three inter-related studies reported in Chapters 4–6 of this thesis.

3.1.3 Methods of processing adherence data

In addition to methods of capturing adherence data, methods of processing adherence data can also influence the calculated adherence levels. Among people with CF, adherence levels for inhaled therapies were generally operationalised as percentages of treatments taken over the expected number of doses as agreed between prescribers and people with CF (or their carers).[4, 162, 171, 175-177] Two studies among people with CF found lower levels of adherence after accounting for potential nebuliser over-use by capping daily maximum use at 100% (i.e. if nebuliser use in a particular day exceeds the agreed regimen, adherence for that day is truncated at 100% to avoid inflating the calculated adherence level) – mean adherence 63% and 47% with capping of daily maximum use at 100% vs 66% and 50% respectively without such adjustments.[178, 179] This is not surprising because EDC showed that some people had periods when they used more medications than prescribed.[4]

This “adjusted” adherence level should, in theory, better reflect effectiveness of medication use since there is no evidence that periods nebuliser over-use can compensate for periods of nebuliser under-use. In other long-term conditions, more sophisticated adherence data processing methods have been employed to calculate adherence levels which reflect “effective medication adherence”; e.g. the model-based metric by Greene et al which accounts for dose-timing errors and inhaler technique errors, in addition to missed doses.[180]

Methods of processing adherence data to reflect treatment effectiveness [181, 182] and the association between adherence and health outcomes have been explored as part of the PhD research, but these details are beyond the scope of this thesis which focusses on the clinical and psychological factors associated with nebuliser adherence among adults with CF. Nebuliser adherence is operationalised as the percentage of total nebuliser doses taken against the agreed dose between clinicians and adults with CF for the three inter-related studies reported in Chapters 4–6 of this thesis. This measure corresponds with the method of quantifying the implementation of a dosing regimen, as outlined by the ABC taxonomy for medication adherence.[156-158]

3.1.4 Setting the scene for the rest of the chapter

Following a brief introduction to medication adherence, this chapter continues by reviewing and summarising the existing literature pertaining to nebuliser adherence among people with CF. In the third section of this chapter, studies without reliable adherence measures and studies looking at potential psychological determinants of adherence pertaining to other CF treatment modalities (i.e. studies excluded from the initial literature review) are summarised. The concept of ‘habit’ as a psychological construct, the relevance of ‘habit’ in other health-related behaviours and methods to measure ‘habit’ are summarised in the fourth section of this chapter. Finally, the gaps in current evidence are summarised and the specific objectives of the remaining chapters to address these gaps are outlined.

Chapter 3, Section 2: A literature review of the clinical and psychological factors associated with nebuliser adherence among people with CF

This literature review sets out to understand the existing literature pertaining to the clinical and psychological factors associated with nebuliser adherence in CF. A secondary aim of this review is to understand the current levels of nebuliser adherence among adults with CF.

3.2.1 Search strategy for the literature review

Electronic Databases search with Embase (from 1947 onwards) and Medline (from 1946 onwards) was performed on 31st January 2016, with the following search strategy:

<Condition-related keyword and MeSH terms> AND <adherence-related keyword and MeSH terms> AND <inhaled therapy-related keyword and MeSH terms>

The condition-related term was:

Cystic fibrosis (MeSH)

The adherence-related terms were:

Medication adherence (MeSH) OR patient compliance (MeSH) OR medication therapy management (MeSH)

The inhaled therapy-related terms were:

Nebulizers or vaporizers (MeSH) OR metered dose inhalers (MeSH) OR dry powder inhalers (MeSH) OR inhaled therapy (keyword) OR nebulized therapy (keyword) OR nebulised therapy (keyword)

Only condition-, adherence- and inhaled therapy-related terms (which map to the patient, problem or population component of the PICO tool [183]) were used in the databases search because the intention is to identify all relevant literature which reported nebuliser adherence levels among people with CF. Hand-searching for relevant literature from the January 2012 to January 2016 editions of the 'Journal of Cystic Fibrosis', 'Pediatric Pulmonology' and 'Patient Preference and Adherence' were performed on 31st January 2016.

Unpublished work was identified by

1. Hand searching the abstract books of both the major international cystic fibrosis conferences (the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference) for 2012–2015 and both the major international respiratory conferences (the European Respiratory Society International Conference and American Thoracic Society Conference) for 2012–2015
2. Google search with “medication adherence” and “cystic fibrosis” as the keywords

Reference tracking of the relevant literature reviews [3, 184] was performed on 31/01/2016. Reference tracking and citation tracking for all the relevant papers retrieved by other search methods were performed on 31/01/2016.

3.2.2 Review procedure for retrieved literature

Studies were included in this review if they fulfil the following inclusion criteria:

- Primary nebuliser adherence data were presented because the focus of this thesis is on nebulised medications, i.e. studies that only measured adherence to dry powder inhalers were excluded
- Methods for capturing adherence data, analysis of adherence data and reporting of adherence levels were adequately described to ensure the reliability of reported adherence levels
- Literature in English language due to the lack of resources for translation

Conference abstracts were included in the review if adequate information were available. Studies were excluded if quantitative adherence data were not reported. Studies were also excluded if the only method for capturing adherence data is via self-report unless ecological momentary assessment technique is used for 'real time' data capture,[185] due to the known lack of reliability with long-term recall based self-reported adherence as discussed in Section 3.1.2.[4, 184, 186, 187] These exclusion criteria were applied since relying on self-reported adherence can easily give rise to misleading conclusions. For example, a study using self-reported adherence measures

concluded that “those involved in the care of patients with cystic fibrosis were able to predict patient compliance”.[188] Studies using more reliable measures e.g. electronic data capture (EDC) or pharmacy refill have shown that clinicians’ “predicted” adherence levels are actually unreliable.[4, 161]

All citations (title and abstract) were screened for eligibility and the following information was extracted from the texts of all eligible literature:

1. Authors and year of publication
2. Study design
3. Study population
4. Method for capturing adherence data
5. Timing and duration of adherence data capture
6. Nebuliser adherence level
7. Associations between adherence and clinical factors
8. Associations between adherence and psychological factors
9. Other relevant findings regarding efforts to support adherence

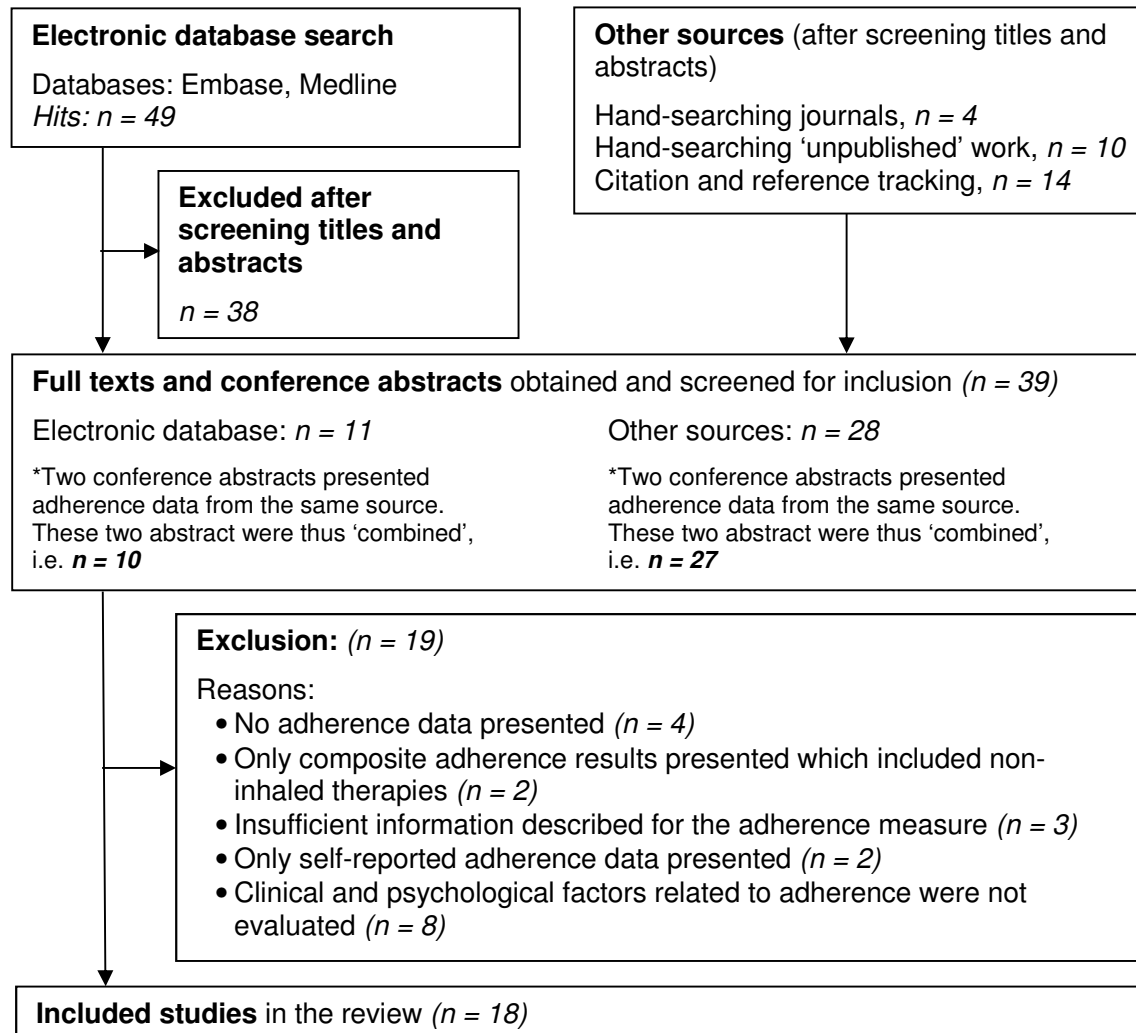
Studies included in this review are either epidemiological observational studies or analysis of data from clinical trials. Given the observational nature of these studies, the methodological quality was assessed using the STROBE statement,[189] with the AHRQ framework used to assess the risk of confounding and bias of the studies.[190] The AHRQ framework consists of 13 questions to assess the risk of confounding, selection bias, performance bias, detection bias, attrition bias and selective outcome reporting.[190] The reliability of the adherence-related results depended not just on the methodology quality of the studies, but also on the methods used to measure adherence. This was evaluated by comparing the different measurement methods used in the studies and taking into account expert opinion from relevant reviews.[184, 191]

The data extracted from the studies have both qualitative (information about study methodology and methods used to measure adherence) and quantitative (adherence levels and association between adherence with clinical / psychological factors) components. Due to the heterogeneous nature of the methods used to measure adherence and relative diversity of the patient population and drugs involved, a meta-analysis of the adherence results was not possible. Therefore, a qualitative synthesis of the relevant data was performed using an approach that mirrors the ESRC methods.[192] The data from individual studies was initially tabulated for preliminary synthesis of findings. Studies were then grouped together based on adherence measurement methods, in order to explore the relationships within the data. A qualitative case description was used to summarise the findings. This narrative analysis of the included studies is similar to the approach used in the most recent Cochrane systematic review of interventions for enhancing medication adherence.[193]

3.2.3 Results of the literature review

Figure 3.1 shows the flow from electronic database search and other 'snow-balling' strategies to study inclusion. In total, 18 studies were included in the review, including 16 journal papers and two conference abstracts.

Figure 3.1: Flow-chart of literature search and study inclusion



The most common method to measure adherence was using pharmacy refill, which was employed in eight studies. Only six studies have objective adherence measure via electronic data capture (EDC). All studies were conducted at high-income, developed countries (UK, US, Canada, Australia, New Zealand). One study was an RCT comparing two different breathing modes of I-neb® (a third generation adaptive aerosol dispenser). Two studies were open label drug studies, whilst the remaining observational studies were either prospective studies (*N* = 8), retrospective studies (*N* = 3) or commercial insurance database analysis (*N* = 4). Table 3.1 summarises the findings for each individual study. Table 3.2 summarises the overall findings of this review.

Table 3.1: Summary of each included study (studies were ordered according to methods of measuring adherence)

Authors, study design	Study population	Methods and duration of adherence data capture	Association between adherence and clinical factors	Association between adherence and psychological factors	Other relevant findings	Overall adherence level [†]	Methodological quality [‡]
Park J, et al [†] ; 2013 [194] Single-centre longitudinal study, UK	Young adults with CF transitioning from children to adult services already on I-neb [®] <i>N</i> = 8 (19 eligible)	Electronic data capture (EDC) via I-neb [®] ; for 1 year pre-transition and 1 year post-transition	Adherence 6-month pre-transition (mean 57%, SD 38) is higher than 6-month post transition (mean 28%, SD 23), <i>p</i> -value 0.011. "Similar trend" with 12-month pre- and post- transition data	N/A	N/A	Mean adherence (EDC): 6 months pre-transition = 57% 6 months post-transition = 28% ^{a,b}	¹ Only 8 participants ² Adherence 12 months pre- and post transition were not reported
McNamara PS, et al; 2009 [176] Single-centre longitudinal study, UK	Children with CF aged 2-15 years established on I-neb [®] <i>N</i> = 28 (48 eligible)	Electronic data capture (EDC) via I-neb [®] ; for 1 year	Similar adherence between Dornase alfa + colistin (mean 67% ± 35%) vs colistin only (mean 64% ± 35) Adherence was better in the evening (mean 75% ± 37%) vs morning (mean 58% ± 34%).	N/A	Change in colistin twice daily to 2 dose once daily improved adherence at month 1 post change, but not sustained at month 3.	Overall mean adherence (EDC) = 60-70% ^{a,b}	¹ Only 28 participants ³ Dornase alfa + colistin may only be prescribed for those who can adhere to both treatments
Ball R, et al; 2013 [171] Two-centre longitudinal study, UK	Children with CF aged 11-17 years established on I-neb [®] <i>N</i> = 24 ("everyone eligible" is in the study)	Electronic data capture (EDC) via I-neb [®] ; for 1 year	21/24 have better weekday adherence (than weekend) 20/24 have better term time adherence (than during holidays) Mean number of nebuliser used was similar for those on 2/day and 3/day at 1.4 day (those on 1/day used mean 0.8 nebuliser/day)	N/A	N/A	Overall mean adherence (EDC) = 65% ^{a,b}	¹ Only 24 participants ³ It may be that 3 nebulisers per day (instead of 2/day) were only prescribed for those whom clinicians believe are able to cope with such treatments
McCormack P, et al; 2011 [175] Single-centre RCT comparing TIM vs TBM after a baseline period of TBM, UK	Children with CF aged 5-16 years established on long-term antibiotics via I-neb [®] (>3 months) in TBM mode for chronic <i>P. aeruginosa</i> infection <i>N</i> = 20 ("everyone eligible" is in the study)	Electronic data capture (EDC) via I-neb [®] I-neb [®] downloaded after 4-6 weeks of baseline (participants randomised to TIM or stay at TBM at this point) and at 8-10 weeks after randomisation	At baseline, there was no statistically significant difference between TIM (mean 86%, SD 11) and TBM (mean 72%, SD 30) Adherence at the end of study shows TIM maintained adherence (mean 89%, SD 8%) but adherence declined in TBM (mean 65%, SD 33). Nebulisation time reduced from 6.9 minutes (SD 2.9) to mean 3.7 minutes (SD 2.3) following switch to TIM.	N/A	N/A	At baseline: Mean adherence (EDC) = 72% for TBM, 86% for TIM End of study, mean adherence (EDC) = 65% ^{a,b} for TBM, 89% for TIM	¹ Only 20 participants ⁴ The random allocation method (using opaque envelope) is susceptible to bias
McCormack P, et al [†] ; 2008 [195, 196] Single-centre cross-sectional study, UK	Children with CF and first / new growth of <i>P. aeruginosa</i> under-going eradication therapy with nebulised colistin via I-neb [®] <i>N</i> = 35 episodes in 33 children (each episode is a unit of analysis)	Electronic data capture (EDC) via I-neb [®] ; for 3 months (which is the duration of eradication period with nebulised colistin).	Adherence better in the evening vs morning, (84% vs 74%, <i>p</i> -value 0.002)	N/A	N/A	Overall mean adherence (EDC) ≈ 80% ^{a,b}	¹ Only 33 participants (although statistically significant difference in adherence between evening and morning sessions were detected) ² Confidence intervals not reported.

[†] = conference abstract

[‡] These adherence levels may over-estimate the real world adherence among adults with CF because: ^a likely selection bias ^b only children included ^c adherence not measured in a real-world setting

[‡] Limitations of the study include: ¹ small number of participants limit the precision of results +/- power to detect between group differences ² selective reporting ³ selection bias ⁴ others

Abbreviations: RCT = randomised control trial; TIM = target inhalation mode; TBM = tidal breathing mode

Authors, study design	Study population	Methods and duration of adherence data capture	Association between adherence and clinical factors	Association between adherence and psychological factors	Other relevant findings	Overall adherence level ¹	Methodological quality ²
Latchford G, et al; 2009 [178] Single-centre cross-sectional study, UK	Adults with CF aged ≥ 18 years only on long-term nebulised colistin via Pro-dose N = 38 (47 invited)	Electronic data capture (EDC) via Pro-dose [®] ; for 3 months Only adherence data for colistin is captured	Higher adherence associated with increasing age (r = 0.348, p-value 0.032), but no correlation with gender, employment or quality of life	N/A	N/A	Overall mean adherence (EDC) ≈ 47% ^a	¹ Only 38 participants ² Only correlation coefficients for age were reported (no confidence intervals). Other correlation coefficients were not reported. ³ Only adherence to a single drug (colistin) is being considered
Shakkottai A, et al; 2015 [177] Single-centre retrospective analysis, US	Children with CF aged 0-21 years prescribed at least 3 months of hypertonic saline / dornase alfa / tobramycin / enzyme / vitamins N = 204 (300 eligible)	Pharmacy refill over 5 years – medication possession ratio (MPR) was calculated 'Modified MPR' = annual MPR instead of MPR over 5 years	Adherence declined with age. <i>Adherence for 0-5yo</i> , median (range): HS (n=37) 80% (12.8-100%) Dornase alfa (n=31) 83.3% (15.4-100%) TSI (n=12) 85.7% (47.1-100%) <i>Adherence for 6-12yo</i> , median (range): HS (n=61) 66.7% (16.4-100%) Dornase alfa (n=37) 72.9% (20.0-100%) TSI (n=19) 66.7% (20.0-100%) <i>Adherence for 13-21yo</i> , median (range): HS (n=49) 54.5% (12.5-100%) Dornase alfa (n=23) 64.7% (14.7-100%) TSI (n=15) 66.7% (40.0-100%)	N/A	Overall group-level adherence levels (modified MPR) were relatively stable over the five year period.	Overall median adherence (MPR) ≈ 65% ^{a,b}	⁴ Relatively stable overall modified MPR may mask variability within specific drugs and within individuals
Quittner AL, et al; 2014 [5] Retrospective analysis of national commercial self-insurance claims database, US	The Thomson Reuters MarketScan Commercial Claims and Encounters Database (January 2005 to June 2011) CF diagnosis in ≥2 visits, ≥1 prescription fill for pulmonary medicines and continuous enrolment for ≥180 days N = 3287	Pharmacy refill over 1 year – medication possession ratio (MPR) was calculated Cumulative MPR (cMPR) calculated as the mean of drug-specific MPR (i.e. azithromycin MPR may be included)	Adherence differed from medication to medication: Dornase alfa mean MPR 57% (n = 2081) TSI mean MPR 51% (n = 1223) AZLI mean MPR 47% (n = 65) Colistin mean MPR 42% (n = 166) HS mean MPR 40% (n = 785) There was a U-shaped relationship between adherence and age, with highest adherence in people aged 6-10 years (median cMPR 63%) and lowest in people aged 26-35 years (median cMPR 42%). There was also consistent increase in cMPR with increasing numbers of prescribed medications (median 35% for 1 medication, n = 1513; median 62% for 5 medications, n = 26). The cMPR included MPR of azithromycin, which is an oral therapy. However, this pattern was consistent for all five types of inhaled therapy. On the other hand, a gender difference in adherence was only observed for azithromycin (male mean 54% ± 34%, female mean 45% ± 35%, p-value <0.001), which is an oral therapy.	N/A	N/A	Mean adherence (MPR): TSI = 51% ^a AZLI = 47% Colistin = 42% Dornase alfa = 57% HS = 40%	³ People prescribed pulmonary medications but not picked up any will not be included in the study ³ It may be that higher number of prescriptions were only prescribed for those whom clinicians believe are able to cope with such treatments

¹ These adherence levels may over-estimate the real world adherence among adults with CF because: ^a likely selection bias ^b only children included ^c adherence not measured in a real-world setting

² Limitations of the study include: ¹ small number of participants limit the precision of results +/- power to detect between group differences ² selective reporting ³ selection bias ⁴ others

Abbreviations: Pro-dose = 2nd generation adaptive aerosol dispenser (I-neb[®] is a 3rd generation adaptive aerosol dispenser); TSI = tobramycin solution for inhalation; AZLI = aztreonam solution for inhalation; HS = hypertonic saline

Authors, study design	Study population	Methods and duration of adherence data capture	Association between adherence and clinical factors	Association between adherence and psychological factors	Other relevant findings	Overall adherence level [†]	Methodological quality [‡]
Nasr SZ, et al; 2013 [197] Retrospective analysis of national commercial self-insurance claims database, US	The Thomson Reuters MarketScan Commercial Claims and Encounters Database (1 Sept 2006 to 31 Aug 2008) ≥4yo with ≥1 claim with CF code and ≥1 claim for dornase alfa continuously enrolled for 12 months pre-index date and 13 months post index N = 907 (1317 excluded as not met the continuous enrolment criterion)	Pharmacy refill over 13 months – medication possession ratio (MPR) was calculated Only dornase alfa adherence data is captured	New users (n = 238) have lower adherence compared to continuing users (n = 669), mean 39%, SD 26%, median 32% vs mean 66%, SD 29%, median 70%, p-value < 0.001 U-shaped relationship with age; mean MPR ± SD: Overall = %59 ± 30% 5-12 years = 66% ± 29% 13-20 years = 57% ± 29% 21-30 years = 54% ± 30% 31+ years = 56% ± 31% (p value < 0.001) Seasonal adherence in mean MPR ± SD: Spring = 59% ± 36% Summer = 56% ± 37% Autumn = 61% ± 35% Winter = 61% ± 34% (p value < 0.001) Similar difference among males & females (mean MPR 59% ± 30%)	N/A	Some differences in MPR according to regions: MPR for North Central 60% ± 30% MPR for Northeast 55% ± 31% MPR for South 58% ± 30% MPR for West 62% ± 28% (p-value 0.285)	Overall adherence (MPR): Mean = 0.59 ^a Median = 0.60	³ People prescribed dornase alfa but not picked up any will not be included in the study ³ Only adherence to a single drug (dornase alfa) is being considered ⁴ Analysis for regional differences in adherence did not account for possible influence of case-mix
Briesacher BA, et al; 2011 [198] Retrospective analysis of national commercial self-insurance claims database, US	The Medstat MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (2001-2006) ≥2 inpatient / outpatient claims with a diagnosis of CF and were continuously enrolled in health insurance with drug coverage for at least 1 year N = 804 (1691 excluded as not on TSI)	Pharmacy refill over 1 year – medication possession ratio (MPR) was calculated Only TSI adherence data is captured	Although TSI is commonly used as treatment among people with <i>P. aeruginosa</i> infection, 352/804 (43.8%) of the study subjects have no coded diagnosis of <i>P. aeruginosa</i> infection. Adherence magnitude was similar among those with <i>P. aeruginosa</i> infection (6% high, 22% medium, 72% low*) and without <i>P. aeruginosa</i> infection (7% high, 23% medium, 70% low*). * 'High' = ≥4 cycles (i.e. adherence ≥67%) * 'Medium' = >2 to <4 cycles (i.e. adherence >33% to <67%) * 'Low' = ≤2 cycles (i.e. adherence ≤33%)	N/A	N/A	Median adherence (MPR) ≤ 33% ^a Adherence categories: Low utilisation = 570 (71%) Medium utilisation = 180 (22%) High utilisation = 54 (7%)	³ People prescribed TSI but not picked up any will not be included in the study
Wertz DA, et al; 2011 [199] Retrospective analysis of national commercial self-insurance claims database, US	HealthCore Integrated Research Database (HIRD) (01 Jan 04 to 31 Mar 09) Aged 0–64 years with ≥2 medical claims for CF and ≥15 months of continuous enrolment (3 months pre-index, 12 months post index) N = 388 TSI users (594 did not fulfil continuity criteria); 444 non users (1114 did not fulfil continuity criteria)	Pharmacy refill over 1 year Only TSI adherence data is captured	Adherence varied according to age ranges: <6 years – 25% high, 42% medium, 32% low * 6-17 years – 35% high, 33% medium, 32% low * 18-40 years – 23% high, 33% medium, 44% low * ≥41 years – 34% high, 37% medium, 29% low * Adherence in females slightly lower than males: Females – 28% high, 35% medium, 37% low * Males – 31% high, 34% medium, 34% low * * 'High' = ≥4 cycles (i.e. adherence ≥67%) * 'Medium' = 2-3 fills (i.e. adherence 33-50%) * 'Low' = 1 fill (i.e. adherence 17%)	N/A	N/A	Mean number of fills = 2.84, i.e. MPR 47.3% ^a Adherence categories: Low n = 139 (35.8%) Medium n = 134 (34.5%) High n = 115 (29.6%)	² The age range used (especially the wide age range covering younger and older adults from 18-40 years) is less helpful to study the relationship between adherence and age ³ People prescribed TSI but not picked up any will not be included in the study

[†] These adherence levels may over-estimate the real world adherence among adults with CF because: ^a likely selection bias ^b only children included ^c adherence not measured in a real-world setting

[‡] Limitations of the study include: ¹ small number of participants limit the precision of results +/- power to detect between group differences ² selective reporting ³ selection bias ⁴ others

Abbreviations: TSI = tobramycin solution for inhalation

Authors, study design	Study population	Methods and duration of adherence data capture	Association between adherence and clinical factors	Association between adherence and psychological factors	Other relevant findings	Overall adherence level [†]	Methodological quality [‡]
Burrows JA, et al; 2002 [161] Single-centre retrospective analysis, Australia	Adults with CF that have had dornase alfa trial N = 77 (115 patients in clinic)	Pharmacy refill over 1 year This was compared against clinician estimation and self-report Only Dornase alfa adherence data is captured	N/A	"There was no difference between reported effectiveness ratings for patients with good, moderate or poor adherence"	N/A	Overall adherence (MPR) = 54% ^a	² Adherence levels according to perceived effectiveness of treatment were not presented. ³ Only adherence to a single drug (dornase alfa) is being considered
Eakin MN, et al; 2011 [200] Single-centre retrospective analysis, US	People with CF aged ≥6 years prescribed with ≥12 months of Dornase alfa, TSI, azithromycin or HS N = 95 (107 consented to be in the study)	Pharmacy refill over 1 year – medication possession ratio (MPR) was calculated Cumulative MPR (cMPR) calculated as the mean of drug-specific MPR (i.e. azithromycin MPR may be included)	Different levels of adherence for different medications: HS MPR (n=25) median 49% (IQR 0-85%) Dornase alfa MPR (n = 90) median ~70% TSI MPR (n = 65) median ~68% U-shaped relationship with age; median cMPR *: 6-12 years ≈ 80% 13-18 years ≈ 72% 19-25 years ≈ 50% 26-34 years ≈ 54% ≥35 years ≈ 74% * Adherence according to age was only reported as cMPR	N/A	N/A	Composite MPR, median = 63% ^a	¹ Statistical significance was not obtained for the comparisons between different medications and for the different age ranges. This might be due to the relatively small sample size (N = 95) rather than a genuine lack of difference
Modi AC, et al; 2006 [162] Two-centre cross-sectional study, US	Children with CF aged 6-13 years with no major co-morbidities (and their care-givers) N = 21 (37 participated out of 227 approached, but only 21 were on nebulised treatment)	1. Parent estimation (3 months) 2. Self-report (3 months) 3. Pharmacy refill over 3 months (medication possession ratio, MPR is calculated) 4. Daily phone diary (DPD) with primary carer – done twice (1 weekday, 1 weekend), covering all the events 24 hours prior to the DPD	Different levels of adherence for different medications: Combined nebulised medications MPR (i.e. dornase alfa, TSI and albuterol) = 68.3% ± 40.7% Dornase alfa MPR (n=25) = 71.7% ± 41.7%	N/A	N/A	Overall adherence, mean (MPR) = 68.3% ^{a,b}	¹ Only 21 participants ² Only a small proportion of people approached participated in the study, and MPR data for nebulised medication only available for 11/21 participants. MPR data for inhaled tobramycin was not reported.

[†] These adherence levels may over-estimate the real world adherence among adults with CF because: ^a likely selection bias ^b only children included ^c adherence not measured in a real-world setting
[‡] Limitations of the study include: ¹ small number of participants limit the precision of results +/- power to detect between group differences ² selective reporting ³ selection bias ⁴ others
Abbreviations: TSI = tobramycin solution for inhalation; HS = hypertonic saline

Authors, study design	Study population	Methods and duration of adherence data capture	Association between adherence and clinical factors	Association between adherence and psychological factors	Other relevant findings	Overall adherence level ¹	Methodological quality ²
Grossoehme DH, et al; 2015 [201] Two-centre cross-sectional study, US	Parents of children with CF aged ≤13yo. N = 87 (142 participated out of 227 approached but only 87 were on nebulised treatment)	Daily phone diary (DPD) with parents – done thrice within 3 weeks (2 weekdays and 1 weekend) covering all events 24 hours prior to the DPD	Neither parental age nor parental education level were predictors for nebuliser adherence (although both factors were predictors for airway clearance adherence) * Low adherers = median 40% * High adherers = median 80% * Super adherers = median 120%	Compared to parents of super adherers* (n = 21), parents of low adherers* (n = 32) reported lower self-efficacy scores (median 1080 vs 1096) but similar intention (median 21 vs 21).	Compared to parents of super adherers*, parents of low adherers* reported increased use of negative religious coping (median 4.5 vs 0.0) and lower body sanctification (median 55.5 vs 62.0) compared to parents of super adherers	Overall mean nebuliser adherence (DPD) = 76% ^{a,b} Adherence categories: ‘Low’ = 32 (36.8%) ‘High’ = 34 (39.1%) ‘Super’ = 21 (24.1%)	³ Only a small proportion of people approached participated in the study
Rosenfeld M, et al; 2011 [202] Three-centre open label evaluation of HS, US & Canada	Infants with CF, aged 12-30 months N = 20 (22 infants screened)	Counting of returned medication vials and daily diary (electronic / paper) with parents; for 2 weeks	Based on daily diary, similar adherence rates recorded were in the morning (median 100%) compared to the evening (median 100%).	N/A	N/A	Overall median adherence (medication count) = 96.1% ^{a,b}	¹ Only 20 participants ³ High adherence rates may be due to short study duration, close observation of participants and selection of highly motivated parents
Zindani GN, et al; 2006 [203] Single-centre cross-sectional study, US	Children with CF on both vitamins and dornase alfa. N = 28 (80 eligible)	Counting of empty medication vials; for 3 months	Dornase alfa adherence: <12yo (n = 14), mean 62.9% (SD 35.4) and median 79.1% (IQR 17.6-100%) ≥ 12yo (n = 14), mean 70.0% (SD 27.0) and median 78.4% (IQR 8.5-100%)	N/A	In the discussion, the authors suggested that disease severity may explain the higher dornase alfa adherence among older children	Overall mean adherence (medication count) = 66.5% ^{a,b}	¹ Only 28 participants ³ Only a small proportion of people approached participated in the study
Oermann CM, et al; 2010 [116] Multi-centre open label trial comparing x2 AZLI doses, US, Canada, Australia & New Zealand	People with CF aged ≥ 6yo and FEV ₁ 25-75% N = 274 (616 people initially screened, 297 people completed the initial phase II trials)	Counting of empty medication vials; for 18 months i.e. the trial period	Similar adherence levels among people in the AZLI twice daily arm (mean 92%) and AZLI thrice daily arm (mean 88%)	N/A	N/A	Overall mean adherence (medication count) = 89.2% ^{a,c}	² No information about data dispersion provided ³ Only a small proportion of people originally screened remained in this study. People with lower adherence may have dropped out of the study

¹ These adherence levels may over-estimate the real world adherence among adults with CF because: ^a likely selection bias ^b only children included ^c adherence not measured in a real-world setting

² Limitations of the study include: ¹ small number of participants limit the precision of results +/- power to detect between group differences ² selective reporting ³ selection bias ⁴ others
Abbreviations: HS = hypertonic saline; AZLI = aztreonam for inhalation solution

Table 3.2: Summary of the narrative synthesis

Aspect of the literature review	Summary
<u>Methodological qualities of the included studies</u>	<ul style="list-style-type: none"> • Nine of the studies are small (<40 participants) and lack the power to detect genuine relationships between adherence and clinical / psychological factors. Four of the larger studies are retrospective analysis of commercial insurance databases, which lack prescription data and may over-estimate adherence. • All 18 studies are susceptible to selection bias since no studies have systematically included the entire cohort within a centre or all participating centres. • Impact of these limitations on the results include: <ul style="list-style-type: none"> i. It is difficult to reliably determine the relationships between adherence and clinical / psychological factors – true relationships may be obscured yet any observed relationships may be spurious ii. Observed adherence levels may be over-estimated
<u>Association between adherence and clinical factors</u> 1. Age 2. Disease severity 3. Gender 4. Socioeconomic status 5. Different inhalation modes of nebuliser 6. Time / other temporal factors 7. Geographic differences in adherence 8. Treatment prescription	<p>A consistent relationship was observed in multiple different studies using different adherence data capture methods – there is a U-shaped relationship between adherence and age, with lowest adherence among younger adults aged 19-25 years (adherence 42-54%) and highest adherence among children aged up to 12 years (adherence 63-80%)</p> <p>Inconsistent relationship observed in different studies</p> <p>Inconsistent relationship observed in different studies</p> <p>Registry analyses have demonstrated that people from more deprived areas in the UK and uninsured people in the US were less likely to be prescribed preventative inhaled therapies. However, there are no studies looking at whether adherence to prescribed therapies differed according to socioeconomic status.</p> <p>A small RCT (20 participants) found that Target Inhalation Mode (TIM) may better sustain adherence compared to Tidal Breathing Mode (TBM)</p> <p>Two studies using electronic data capture (EDC) among children with CF found higher adherence levels in the evening. Another study using EDC among children with CF found higher adherence during weekdays (vs weekends) and term-time (vs holidays). A study using pharmacy refill found lower adherence in the summer compared to other seasons.</p> <p>A study found differences in adherence according to geographic locations but this evidence is inconclusive since potential differences in case-mix were not accounted for in the analysis.</p> <p>Within a cohort, there is a varying degree of adherence to different inhaled therapies. Heterogeneity between studies meant it is not possible to draw a conclusion regarding the overall adherence level to any specific treatment. Three studies found that adherence did not decrease as the number of prescribed medications increased, but two of these studies are observational and may be confounded by indication bias (more treatments may only be prescribed for those able to cope with increased 'treatment burden').</p>
<u>Association between adherence and psychological factors</u>	<p>Only two studies evaluated the potential influence of psychological factors:</p> <ol style="list-style-type: none"> 1. One study (using pharmacy refill) found no association between <i>perceived effectiveness</i> of the treatment and adherence. 2. One study (using daily phone diary) found similar <i>intention</i> regardless of adherence, but lower <i>self-efficacy</i> was associated with lower adherence.
<u>Adherence levels among adults with CF</u>	<p>Seven studies evaluated adherence among adults with CF (one with EDC, the remaining six studies with pharmacy refill) found median adherence levels of 30-50% in real-world settings.</p> <p>This contrasted with mean adherence level of 89% (measured by counting empty medication vials) in an open label drug trial.</p>

3.2.3.1 Methodological limitations of reviewed studies

Nine studies recruited fewer than 40 participants from a single centre (or two centres), hence those studies have limited precision in detecting relationships between adherence and clinical / psychological factors. Four of the larger studies (with 388 to 3287 participants each) are retrospective analysis of commercial insurance databases in the US. It is impossible to determine the exact prescription of the participants in those studies,[5, 197-199] hence people with CF on nebulised medications who do not collect any of their medications (i.e. adherence = 0) were not included. This may reduce the power to detect association between adherence and clinical / psychological factors; and also over-estimate nebuliser adherence levels.

None of the 18 studies has systematically included the entire cohort within a centre or all participating centres. Therefore, these studies are susceptible to selection bias, whereby people with poor adherence and poor engagement with the clinical team are less likely to be recruited, hence over-estimating the actual real-world adherence levels. The selection bias (or lack of genuine representativeness) may also impact on the observed relationship between adherence and clinical / psychological factors.[204] For example, if most people with high levels of depression were not included in a study, the study may well be under-powered to detect the relationship between adherence and depression even if large numbers of participants were recruited.

The heterogeneity of the methods to capture adherence data, duration of data capture and methods of calculating adherence is another important limitation. The heterogeneity of measured adherence and different factors influencing adherence that were investigated meant it was not possible to pool different studies in a meta-analysis. The lack of standardisation in the methods to calculate adherence also meant that differences in adherence level between studies could simply be due to data issue rather than genuine differences in adherence between different populations. Results from different studies were interpreted in the context of these limitations, and adherence levels between different populations (e.g. the UK vs the US) were therefore not directly compared.

3.2.3.2 How is adherence related to age?

Eight studies looked at the influence of age on adherence. In general, children have higher adherence levels compared to adults, and younger adults tended to have the lowest adherence levels.

Four studies included people with CF with a wide age range (both children and adults).[5, 197, 199, 200] All four studies used medication possession ratio (MPR) as the adherence measure and found a U-shaped relationship between adherence and age, with lowest adherence among younger adults (aged 19-25 years; adherence 42-54%) and highest adherence among younger children (aged up to 12 years; adherence 63-80%).

A study among adults with CF used electronic data capture (EDC) as the adherence measure and found increasing adherence with age (adherence ~47% for everyone in that study).[178] The other study which used EDC followed up adolescents who transitioned from children to adult services and found a decline in adherence from a mean of 57% pre-transition to 28% post-transition.[194] A

study among children which measured adherence using MPR found lower adherence among older children (median adherence ~83% among children aged 0–5 years; median adherence ~60% among children / adolescents aged 13 to 21 years).[177] Another study measured adherence by counting empty medication vials over a 3-month period and found similar dornase alfa adherence among children aged ≥ 12 years (median adherence 78.4%) and < 12 years (median adherence 79.1%).[203]

3.2.3.3 What is the impact of disease severity?

The authors of the study which found similar dornase alfa adherence among children aged ≥ 12 and < 12 years speculated that older children might have higher adherence due to more severe lung disease.[203] However, none of the 18 studies that were included in this review evaluated the relation between adherence and %FEV₁ (which is generally accepted as the most important marker for the severity of lung disease in CF [205-208]). Another study found no differences in MPR for nebulised tobramycin among people with *P. aeruginosa* infection (who typically have more severe lung disease) vs people without *P. aeruginosa* infection.

3.2.3.4 Is there a gender difference in adherence?

Potential gender differences in adherence are of interest because a study using self-reported adherence measure found lower adherence among adolescent females with CF, and that CF had a greater emotional impact on adolescent females compared to adolescent males.[209]

Three studies using MPR as the adherence measure evaluated the relationship between gender and nebuliser adherence. A study found slightly lower adherence among females (28% with adherence $\geq 67\%$ compared to 31% among males),[199] whilst two other studies found no gender difference in adherence for nebulised medications.[5, 197] Another study using EDC as the adherence measure also found no gender difference in adherence.[178]

Therefore, studies using more reliable adherence measures do not provide any compelling evidence of a gender difference in adherence, but numbers are small and study quality is low. Thus there is an absence of evidence, rather than evidence of absent gender difference.

3.2.3.5 Is there evidence that socioeconomic status influence nebuliser adherence?

A UK CF registry analysis found that people from more deprived areas were less likely to be prescribed preventative inhaled therapies,[150] and this is mirrored by a recent US CF Foundation Patient Registry analysis which found that uninsured adults with CF were less likely to receive preventative inhaled therapies.[151]

However, the direct impact of socioeconomic status (or insurance status in the US) on medication adherence has not been directly evaluated. A study using daily phone diary as the adherence measure among 87 children with CF found that neither parental age nor education level influenced nebuliser adherence.[201] However, both these factors were associated with adherence to chest physiotherapy in that study.[201] Thus the evidence is inadequate to draw firm conclusions about the relationship between socioeconomic status and nebuliser adherence.

3.2.3.6 What is the impact of different inhalation modes?

I-neb® was designed to deliver aerosol with two different breathing pattern algorithms: (1) Tidal Breathing Mode (TBM) in which users inhale spontaneously throughout tidal breathing with pulsing of aerosol depending on flow rate and volume of the breathing pattern; (2) Target Inhalation Mode (TIM) in which user is guided into a slow and deep inhalation to reduce treatment times and optimise lung deposition.[210] A randomised clinical study among 20 children found that children in the TIM arm maintained their adherence (mean 86% at baseline, mean 89% at four weeks post randomisation) while children in the TBM arm showed a decline in adherence (mean 72% at baseline, mean 65% at four weeks post randomisation).[175]

3.2.3.7 What is the temporal variation in adherence? – time of day, weekdays vs weekends, holidays / seasonal effects

Data-logging nebulisers such as the I-neb® also allowed the detailed study of variation in adherence. Two studies using EDC among children with CF found higher adherence levels in the evening (mean 75% and 84%) compared to the morning (mean 58% and 74%).[176, 195] Another study using EDC among children found that most children (21/24, 87.5%) have better adherence during the weekdays compared to weekends, and most children (20/24, 83.3%) have better adherence during term time compared to holidays.[171]

Alternative adherence measures are more limited in terms of studying variation in adherence (see Section 3.3). A study among infants with CF using parent self-reported adherence captured by daily diary found a recorded (by parents) median adherence of 100% for both morning and the evening sessions.[202] A large study using MPR did find seasonal effects in adherence, with slightly lower adherence in the summer (mean 0.56) compared to other seasons (mean 0.59 – 0.61) which the authors attributed to summer holidays.[197]

3.2.3.8 Is there geographical variation in adherence?

As mentioned in Section 3.2.3.1, retrospective analysis of commercial insurance databases allowed adherence to be studied among larger groups of people with CF. One such study found greater differences in adherence according to geographic locations (e.g. mean MPR for West region was 0.62 whereas mean MPR for North East region was only 0.55) compared to the seasonal difference described in Section 3.2.3.7.[197] This suggests that perhaps adherence to preventative inhaled therapies differed according to specialist CF centres, although it should be noted that the regional analysis did not account for potential differences in case-mix.

3.2.3.9 What is the influence of prescription on adherence?

Studies using MPR as the adherence measure were able to describe adherence levels for different preventative inhaled therapies.[5, 162, 177, 200] Within a cohort, adherence differed according to the type of inhaled therapies. However, there were no consistent patterns between different cohorts of study subjects. For example, three studies found highest levels of adherence with

dornase alfa [5, 162, 200] but another study found higher adherence levels to nebulised tobramycin compared to dornase alfa (median ~75% vs median ~70%).[177]

However, perhaps surprisingly, different studies using different adherence measures consistently found no evidence of lower adherence with increased number of medications or doses prescribed. An open label drug trial found similar adherence levels among people on twice daily (mean 92%) and thrice daily (mean 88%) Aztreonam for inhalation solution by counting empty medication vials.[116] A large study even found a consistent increase in MPR with increasing numbers of prescribed medications, e.g. median MPR of 35% for people prescribed x1 type of pulmonary therapies and median MPR of 62% for people prescribed x5 types of pulmonary therapies).[5] A study using EDC also found similar adherence among children prescribed 3 doses of inhaled medications per day i.e. colistin twice daily and dornase alfa once daily (mean 67%) and 2 doses of inhaled medications per day i.e. colistin twice daily only (mean 64%).[176] When colistin prescription was changed from one dose twice daily to two doses once daily, adherence improved at Month 1 but improvement was not sustained at Month 3.[176]

3.2.3.10 What psychological factors are associated with nebuliser adherence?

Only two out of the 18 studies evaluated the potential influence of psychological factors. One study using MPR as the adherence measure among 77 adults with CF reported that there was no association between *perceived effectiveness* of dornase alfa and adherence.[161] Another study using daily phone diary as the adherence measure among 87 children with CF aged ≤13 years found that parents reported similar *intention* (i.e. the motive of performing a behaviour) regardless of adherence, but lower *self-efficacy* (i.e. belief in one's ability to perform a behaviour) scores were associated with lower adherence.[201]

3.2.4 Discussion

This literature review has four main findings.

First, among the several clinical (i.e. demographic / treatment) factors potentially influencing nebuliser adherence that were explored, only age has a consistent relationship with adherence. Adolescents and young adults tended to have the lowest adherence levels. Increasing adherence levels among older adults [5, 178, 199, 200] may be a function of age (e.g. increased maturity [211]) but may also reflect survival bias (if people with higher adherence levels also live longer).

Second, current evidence, albeit not extensive, suggests that “treatment burden” (which is often operationalised as the duration, frequency and complexity of treatment regimens) does not offer a sufficient explanation for low adherence among people with CF. Similar adherence levels were observed with different number of types or doses of inhaled medications. One study even found a consistently increasing levels of adherence with increasing numbers of prescribed pulmonary medications,[5] although it may be that people with higher adherence were being prescribed more

treatments as they are perceived as being able to take them.[212] Older adults tended to have more complex treatment regimens compared to younger adults,[213] but older adults also have higher adherence levels. Simplifying treatment regimen by altering twice daily colistin to two doses once daily did not result in sustained adherence improvement.[176] Another study found that adolescents with CF were most adherent during term-time and weekdays when they are likely to be busiest (thus most susceptible to lapse due to “treatment burden”).[171] A potential explanation for this observation is that routine is more regimented during school days and more lax during weekends or holidays.

Third, real world nebuliser adherence among adults with CF is lower than adherence observed in controlled clinical trials. Various controlled clinical trials in CF reported nebuliser adherence levels of 80-100%.[116, 214-216] This review found a real world nebuliser adherence level of around 35-75% among people with CF. Among adults, median adherence is only around 30-50%. The real-world nebuliser adherence figures in this literature review are mostly derived from larger studies based on pharmacy refill data collected in commercial insurance databases.[5, 197-199] It has been estimated that administrative databases could over-estimate adherence by 25% because prescription data are unavailable, hence administrative databases fail to capture people who did not even fill the first prescription (i.e. adherence = 0%).[217] MPR data have also been shown to over-estimate adherence when compared against EDC data in other CF treatments.[167] Adherence figures from the US may be perceived as less reliable because copayment is thought to discourage adults with CF from collecting prescribed medications. However, a recent large study (10,563 study subjects) on cost sharing among patients with acute coronary syndrome found no improvement in adherence rates.[218] Indeed, pharmacy refill data among adults with CF in Australia [161] and a recent study among 106 adults in the UK (where prescription cost is not an issue) [219] also found adherence levels of only 50-60%. Given that preventative inhaled therapy would only work if they are used appropriately, this level of adherence would imply that the CF population is not deriving the optimal health benefits observed in controlled clinical trials. Two recent UK CF registry analyses (undertaken as part of the PhD research) highlighted the real-world consequences of low adherence among adults with CF. The first analysis identified a group of adults with high year-on-year intravenous antibiotics use, even among those with FEV₁ ≥70%, which suggests a reliance on rescue therapies to compensate for low adherence with preventative inhaled therapies.[220] The second analysis demonstrated that adult CF centres are still dependent on higher intravenous antibiotics use to achieve better FEV₁, despite the increasing availability and prescription of preventative inhaled therapies.[79] Of note, low levels of adherence are also pervasive in other long-term conditions. It is estimated that only around 50% of all medications are taken as recommended, leading to increased morbidity and excess mortality which is estimated to cost around US\$100 billion per year.[221-228]

Fourth, the reviewed studies looking at adherence interventions [175, 176] have not demonstrated clear evidence of improving adherence. In other long-term conditions, there is meta-analysis

evidence that feedback of objective adherence data is associated with improved adherence.[229] This literature search found only one published study which evaluated feedback of objective adherence data (captured via I-neb[®]), which is a before and after study among 28 children with CF.[230] Children who independently uploaded data maintained median adherence of 100% over two months ($N = 3$). Children who uploaded data with prompting showed a relative increase in adherence of 111% (baseline median adherence of 38%; $N = 10$). Children with no data upload showed a relative increase in adherence of only 7% (baseline median adherence of 71%; $N = 15$). However, these differences may be the result of people with improving adherence being more willing to upload and share their data, instead of feedback improving adherence. Another 'intervention' which is expected to increase adherence would be a period of hospitalisation to concentrate on adherence, since a hospitalised person with CF should receive more attention from clinical staff and should have fewer distractions. However, adherence levels during hospitalisations are surprisingly low. A study which evaluated I-neb[®] adherence among 12 children with CF during their hospitalisations found a median adherence of only 51%.[231] This adherence level is lower compared to adherence levels among children with CF in general, perhaps suggesting that children that required hospitalisation have lower adherence levels. It is nonetheless important to note that hospitalisation alone does not guarantee the use of nebulisers. In hospitals, even a nurse handing a medication to patients does not necessarily equate to the medication being used – another recent study using I-neb[®] also found unexpectedly low levels of adherence (mean 62%) among hospitalised children with CF even though the prescription charts recorded 100% of nebulised medications as being administered.[166]

This literature review has several limitations. Only studies published in the English language were included. Generalisability of the findings in non-developed countries is uncertain, since all included studies were conducted at developed countries. Authors of relevant abstracts were not emailed to obtain further data and the search for unpublished studies was not comprehensive. Possible publication bias meant that any observed associations may be spurious or exaggerated;[232, 233] though the literature review did identify studies with conflicting results which suggests that manuscripts highlighting a lack of association were still being submitted and published. Literature search and review were only performed by a single person; hence several studies may be missed or inadvertently excluded. The electronic databases search were limited by the use of mainly MeSH terms, hence more studies were found with 'snow-balling' strategies compared to databases search. In addition, three large RCTs evaluating adherence interventions have recently been completed but full results are yet to be published (see summary of these studies in Table 3.3).[234-236] Consequently, these studies were not included in this review. None of the studies used EDC to capture adherence data and their results are unlikely to invalidate the main conclusions of this review. A meta-analysis could not be performed due to the heterogeneity of the included studies, and limitations of narrative synthesis are acknowledged.[192]

Table 3.3: Summary of three large RCTs evaluating adherence interventions among people with CF that have been completed but full results are yet to be published

I Change Adherence and Raise Expectations (iCARE) Study [234]

Design: Cluster RCT, 2-arm, 18 centres across the US

Participants: Adolescents with CF aged 11-20 years on ≥ 1 type of respiratory therapy, $N = 607$

Intervention: Comprehensive adherence programme (CAP) – education + problem solving

Comparator: Usual care

Outcomes: Primary – composite adherence to chronic pulmonary medications (nebulisers + azithromycin), measured as MPR[†]

Secondary – %FEV₁, pulmonary exacerbations, quality of life

Interim results: Adherence (MPR[†]) at 12 months – Intervention group, i.e. CAP ($N = 154$), median 54% (IQR 28 – 72%)

Comparator group, i.e. usual care ($N = 140$), median 52% (IQR 28 – 71%)

Cell phone intervention to improve adherence (CFfone) [235]

Design: 2-arm parallel RCT, multi centre

Participants: Adolescents with CF aged 11-20 years and have regular internet access, $N = 95$

Intervention: CF Fone – secure website providing behavioural & medical information with social networking features

Comparator: website with CF information

Outcomes: Primary – CF knowledge

Secondary – adherence (measured as MPR[†]); quality of life

Interim results: Adherence levels not yet reported; quality of life similar for both arms

Building Adherence to Live With And Navigate my CF Experience (BALANCE) [236]

Design: 2-arm parallel RCT (comparing x2 types of adherence interventions), single centre

Participants: Adults with CF aged ≥ 16 years on chronic respiratory therapy, $N = 128$

Intervention 1: Motivational interviewing (MI)

Intervention 2: Education + problem solving (EPS)

Outcomes: Primary – composite adherence to chronic pulmonary medications (nebulisers + azithromycin), measured as MPR[†]

Secondary – change in %FEV₁

Interim results: Adherence (MPR[†]) at 12 months – Intervention 1 group, i.e. MI ($N = 44$), median 54% (IQR 37 – 73%)

Intervention 2 group, i.e. EPS ($N = 51$), median 51% (IQR 17 – 71%)

[†] MPR = medication possession ratio. Composite MPR was calculated by averaging MPR of all individual chronic pulmonary medications.

Nonetheless, this review has identified several notable gaps in the current evidence base; not least of which is an absence of adequately powered prospective studies explicitly designed to objectively explore adherence using EDC data. EDC is generally considered the ‘gold standard’ measure to capture adherence data,[168] but clinical (i.e. demographic / treatment) factors that may influence adherence have not been systematically explored using EDC adherence data. For example, there has been no study using EDC to explore the impact of socioeconomic status on adherence. “Treatment burden” is the focus of many CF-related studies,[213, 237-244] yet the impact of continuous vs alternating inhaled antibiotics regimen (which is an important factor that influences complexity of treatment regimen [245, 246]) on adherence also has not been explored.

Only two studies have evaluated a limited range of potential psychological factors that may influence adherence using (relatively) accurate adherence measures,[161, 201] even though psychological factors are likely to be more proximal determinants of adherence compared to clinical factors.[247] As described in Section 3.1.2, studying adherence using self-reported data may result in misleading conclusions because self-report is so unreliable. A recent study identified different predictors of medication adherence by using different adherence measures (self-report vs EDC).[248] This study was a secondary analysis using data from two randomised control trial of adherence interventions among patients with Type II diabetes and rheumatoid arthritis. Age was found to be the only predictor of adherence using the Morisky Self-Report Scale (increasing age was associated with higher adherence); but gender and income were the only predictors of adherence using the Aardex Medication Event Monitor, which is a form of EDC (female tended to have higher adherence and annual income <\$10k was associated with the lowest adherence). This finding highlights the need for more studies exploring the relationship between adherence determinants and adherence using accurate EDC data.

Due to the paucity of existing literature which relates objective adherence data to psychological determinants, relevant qualitative literature or studies that explored determinants of adherence using self-reported adherence are summarised in the next section of this chapter (Section 3.3). Another evidence gap is the lack of studies evaluating the relevance of 'habit' (i.e. automatically experiencing an urge to perform a behaviour in certain settings) in sustaining medication adherence among people with CF. In other long-term conditions, habit has been shown to better predict medication adherence compared to conscious motivational factors e.g. treatment beliefs,[7-11] albeit these are studies using self-reported adherence. A recent meta-analysis of 771 medication adherence intervention studies also identified habit as a promising target for intervention.[249] Therefore, Section 3.4. discusses the potential role of habit in nebuliser adherence and considers how habit can be measured, by drawing heavily on a recent habit scoping review.[250] Finally, the evidence gaps are summarised and the steps taken to address these gaps in the subsequent chapters are outlined in Section 3.5.

Chapter 3, Section 3: A review of other factors that may influence nebuliser adherence

Studies not grounded on reliable adherence data or studies not related to nebuliser use were excluded from the literature review in Section 3.2 to avoid conflating studies with different methodological robustness. Misleading conclusions can be reached by using inaccurate data e.g. self-reported adherence data. For example, a recent study identified different predictors of medication adherence by using different adherence measures (self-report vs EDC).[248] It is likely that simply ascertaining a list of barriers or facilitators without triangulation with accurate adherence data can also be misleading.

However, the strict exclusion criteria for the literature review in Section 3.2 meant that only two studies evaluating potentially relevant psychological factors were included. To obtain a broader overview of the current CF literature, this section summarises qualitative literature or studies that explored determinants of adherence using self-reported adherence. In this section, relevant studies related to other CF treatment modalities are also included.

3.3.1 “Forgetting”

“Forgetting” has been identified as a significant barrier to using nebuliser among people with CF in two qualitative [251, 252] and three quantitative studies.[245, 253, 254] Both intentional and unintentional forgetting were identified in a qualitative study.[251]

Studies in other long-term conditions have demonstrated that “forgetting” is rarely a random event; instead it may be under-pinned by other factors e.g. treatment beliefs.[255, 256] Within a comprehensive behavioural framework e.g. the COM-B model (Capability, Opportunity, Motivation and Behaviour), “forgetting” may be the outcome of impaired cognition (psychological capability), change to daily lifestyle (physical capability) or absence of cue for action (automatic motivation).[257] Thus, the term “forgetting” is essentially a reiteration of the problem and holds no explanatory value. Simply identifying “forgetting” as a barrier without delving deeper into the actual cause of forgetting is unhelpful in understanding adherence or to develop an effective adherence intervention.

3.3.2 “Treatment burden”

A recent James Lind Alliance Priority Setting Partnership has identified “effective ways of simplifying treatment burden” as one of the top 10 research priorities in CF.[258] “Treatment burden”, often operationalised as the duration, frequency and complexity of treatment regimens, has been identified by various qualitative and quantitative studies as being particularly problematic for nebuliser use.[245, 251-253, 259] The treatment demands placed upon people with CF has been described as “extraordinary when compared with most other chronic illnesses”. [260] People with CF reported spending 2-3 hours daily preparing and using treatments, with airway clearance and inhaled therapies particularly time-consuming.[239, 243]

Various competing social and work demands were reported, and time pressures were identified in various qualitative and quantitative studies.[245, 251-254, 259] Managing competing priorities is a challenge [251, 252] and the trade-off may be to miss medications every few days or when busy.[245] Adding to treatment burden is the potential inconvenience associated with access to medications, such as the cost of medications and the need to obtain some medications from hospital pharmacies (instead of community pharmacies).[259]

3.3.3 Are dry powder inhalers the solution to CF adherence?

Dry powder inhalers e.g. mannitol, colistin dry powder and tobramycin dry powder are specifically marketed around their ability to alleviate “treatment burden” due to shorter inhalation duration and these inhalers do not require cleaning.[261-264] A discrete choice experiment suggested that an “average” adult with CF considered reduced time burden to be twice as important as side-effects from using treatments e.g. dry cough.[240] A time trade-off survey suggested that an “average” adult with CF would be willing to give up 5.3 years of life (out of 40 years) just to use dry powder inhalers.[244]

Short-term adherence to tobramycin dry powder inhalers among 78 adults at the Cork Adult CF Centre may seem promising but it is important to recognise that the adherence was estimated via self-report. The number of adults approached to try dry powder inhalers was not presented in the paper, but around 140-150 adults with CF received care at Cork.[265, 266] Among participants previously using nebulised tobramycin (TIS) who were switched to use dry powder tobramycin (TIP) for 12 months, TIP adherence at month 12 (31/40, 77.5% self-reported adherence $\geq 80\%$ with TIP) was significantly higher compared to baseline TIS adherence (22/49, 44.9% self-reported adherence $\geq 80\%$ with TIS).

However, longer-term data are not promising. Data from Cardiff showed that around 50% of adults who trialled dry powder inhalers discontinued after 4-5 months due to intolerance.[267] Data from Birmingham showed that only 58/130 (45%) of the adults initially prescribed TIP remained on TIP after 29 months, with most common causes of discontinuation being side-effects e.g. cough or chest discomfort.[268] MPR among those still on TIP was only around 65%.[268] Recent data from Leeds showed that MPR was somewhat higher for nebulised antibiotics (mean $\sim 65\%$) compared to dry powder antibiotics (mean $\sim 62\%$).[219] A recent analysis of national commercial self-insurance claims database in the US found no differences in adherence (as a continuous variable) between TIP and TIS even after various adjustments (mean numbers of medication cycles collected over 1-year were 3.85 vs 3.65, which roughly equate to MPR of 64.2% vs 60.8% since each adult would be using 6 cycles of tobramycin per year with an alternating regimen).[269]

It has been argued that people with CF would only recognise that a particular treatment is quick and easy if they had used a previous version that was slower and harder, thus provision of quick easy treatment as first line would result in the same adherence levels as older harder treatments.[270] A more pertinent point is that “treatment burden” cannot solely be a function of the treatment. Perceived burden would involve interaction between the treatment and the person using the treatment. A person prescribed only one pulmonary medication may still find the treatment burdensome and achieve an adherence level of 35% whilst another person prescribed five pulmonary medications may not find managing those treatments burdensome and achieve an adherence level of 62%. Indeed, a large study found a consistent increase in MPR with increasing

numbers of prescribed medications, e.g. median MPR of 35% for people prescribed x1 type of pulmonary therapies and median MPR of 62% for people prescribed x5 types of pulmonary therapies.[5]

As discussed in Section 3.2.4, it is unlikely that “treatment burden” offers a sufficient explanation for low adherence among people with CF. Ivacaftor (which only involves swallowing tablets twice daily) is far “less burdensome” than dry powder inhalers but EDC data showed an ivacaftor adherence level of ~60%.[167] Dry powder inhalers have not solved the adherence problem in asthma (whereby EDC data also show adherence levels of 50-60% [271, 272]) and it seems unlikely that they will be the magic bullet solution for low adherence among people with CF.

3.3.4 Organisation / structure / routine

People with CF have reported that being organised and establishing a structure (e.g. having a regular and predictable schedule) and having a routine (i.e. fostering contextually stable behaviours and persistent behavioural pattern) facilitate the use of medications.[251, 252, 259] People have also described finding treatments “a lot easier” when they have a routine.[251] This raises the possibility that developing a routine may help to moderate the perceived difficulty or “burden” of using preventative inhaled therapies.

3.3.5 Disease severity

People with CF tend to be more symptomatic (e.g. have frequent cough productive of sputum and shortness of breath) with increasing lung disease severity. Presence of symptoms could motivate people to use their treatments [251, 252] whilst the absence of symptoms could potentially discourage people from using their treatments regularly.[245, 251] However, increasing disease severity also meant more fatigue, and this can result in treatments being omitted.[251, 259]

Quantitative studies evaluating severity of disease as a predictor for adherence have found conflicting results.[188, 273]

3.3.6 Perception of illness and treatment effects

The conflicting results for disease severity as a predictor of adherence may be in part due to people under-estimating the severity of their illness.[66] Thus, perception of illness may be more relevant than the actual severity of disease in terms of influencing adherence.

A quantitative study among children with CF found that perception of more severe disease or increased susceptibility to recurrent infection was strongly correlated with higher self-reported adherence to inhaled therapies.[274] Among adults with CF, the results are less convincing. A quantitative study found that no relationship between perception of disease severity and reported

adherence to pancreatic enzyme replacement therapy or exercise (adherence to inhaled therapies was not evaluated);[275] although another study found those who perceived their illness to be less severe reported slightly lower levels of adherence.[276]

A qualitative study suggested that people may also be discouraged from using their medications if they perceive it as futile and expressed preference to pursue other activities if life may be limited.[252] Other qualitative studies found stronger desire to use treatments among people who experienced benefit from the treatment (e.g. if regular use of medications kept them out of hospital [259]), or if non-adherence resulted in worsening of symptoms.[251] Participants in a qualitative study reported that side-effects were not an important barrier to using treatments, although side-effects may result in missed doses.[259] However data are not consistent and some empirical data suggest that side-effects may be an important cause of treatment discontinuation (see Section 8.1.3.3).[267, 268]

3.3.7 Beliefs about treatments

The Beliefs about Medication Questionnaire (BMQ) has been used among adolescents with CF to evaluate their beliefs about the necessity of treatments and their concerns about potential adverse effects.[277] This study found that low self-reported adherence levels to inhaled antibiotics were associated with lower necessity scores and believing that CF is not amenable to treatment.[277]

Another study used BMQ among parents of children with CF, and found that adherence to pancreatic enzyme replacement therapy and chest physiotherapy (adherence to inhaled therapies was not evaluated) was also related to parental necessity beliefs (rather than concerns about potential adverse effects).[278]

A qualitative study found that lack of immediate impact from treatments or feeling well may reduce the belief that treatments are necessary.[252] Qualitative studies also found that not everyone views preventative inhaled therapies as important.[252, 259] Another study reported that “guilt” from non-adherence, even if there was no immediate impact on symptoms, might encourage the use of treatments.[251]

3.3.8 Knowledge of disease and treatment

Education-based counselling or information provision is often used as an adherence intervention in CF [15, 279] because previous studies have identified gaps in knowledge.[280] A recent quantitative study among adolescents with CF found that disease knowledge was only correlated with MPR to nebulised hypertonic saline but not with MPR to nebulised dornase alfa.[281] Another recent quantitative study among adults with CF found no correlation between disease- or treatment-related knowledge and self-reported adherence to inhaled therapies.[282]

3.3.9 Psychopathology

A recent large epidemiological study (6088 people with CF and 4102 parents) found *higher levels* of depressive symptoms (10% of adolescents, 19% of adults) and anxiety (22% of adolescents, 32% of adults) among people with CF compared to the general population.[283] However, another recent large epidemiological study in the UK (2065 people with CF) found *similar levels* of depressive symptoms (~3% of adolescents, ~12% of adults) and anxiety (~20% of adolescents, ~33% of adults) among people with CF compared to the general population.[284]

A study has found that children and parents with depression had lower adherence to chest physiotherapy [285] although another study failed to demonstrate this association.[278] Studies evaluating the impact of depression or anxiety on adherence to inhaled therapies were also inconclusive, in part because studies were small and adherence were measured using self-report. A study among 52 people with CF found that children and adolescents with anxiety disorders (diagnosed with DSM-based interviews) actually had higher levels of reported adherence.[286] A recent study among 67 people with CF found that adults with depressive symptoms (measured with Major Depression Inventory, MDI [287]) had lower levels of reported adherence.[288] Another study found that participants with depressive symptoms (measured with Center for Epidemiologic Studies Depression scale, CES-D [289]) reported lower medication beliefs and has lower adherence (as measured by composite MPR which included inhaled therapies and oral azithromycin).[290]

3.3.10 Other psychological factors

The study that evaluated the relationship between depressive symptoms, adherence and treatment beliefs used a measure of 'medication beliefs' that included measures for self-efficacy, motivation, perceived importance and outcome expectancies from taking the medication.[290] Among these four measures, self-efficacy was most strongly associated with medication adherence.[290] Structural equation modelling found that the impact of depressive symptoms on medication was mediated by medication beliefs in that depressive symptoms was associated with less positive medication beliefs but did not directly reduce medication adherence.[290]

However, the relevance of self-efficacy as a determinant of nebuliser adherence remains uncertain. A recent quantitative study among adolescents with CF found no association between self-efficacy and adherence to inhaled therapies (as measured by MPR).[281]

3.3.11 Ways of coping with CF

A study found that people with CF who reported high external control (that is attributing success to luck or fate, or efforts of others, i.e. little personal control over the course of CF) also reported higher levels of overall treatment adherence.[291] Perception about locus of control may relate to people's coping mechanisms.

A study found that people who scored highly on the optimistic acceptance and hopefulness scales also reported higher levels of adherence with pancreatic enzyme replacement therapy and chest physiotherapy (adherence to inhaled therapies was not evaluated).[292] On the other hand, avoidance strategies (e.g. denial) were associated with lower levels of self-reported adherence.[292] Since self-report is poorly calibrated to the actual adherence levels,[4] it is possible that a person's coping characteristics influenced the reporting of adherence rather than actually reflecting objective adherence.

3.3.12 Family relationship

Family dynamics and relationships are likely to be an important determinant of adherence, especially among children with CF who rely on parents to deliver treatments. Two quantitative studies found that better observed family functioning were associated with higher reported adherence among children with CF.[293, 294]

Parental supervision tended to decline from early to late adolescence, which may contribute to lower medication adherence.[295] However, a qualitative study focussing on adolescents with CF suggests that early development of self-care skills in children, then a gradual shifting of responsibility for treatments to adolescents can facilitate adherence.[252] Parents who were able to engage in open conversations about adherence with their children may better support adherence, compared to parents who were unwilling to cede control.[252] There was also a suggestion that allowing adolescents to experience negative health consequences of non-adherence may increase likelihood of future treatments.[252]

Supports and reminders from parents are considered important,[251] even among adults with CF.[259]

3.3.13 Other social relationships and the stigma using treatments

A quantitative study found that both friendships with positive traits (e.g. companionship, support) and negative traits (e.g. criticism, conflict) among adolescents with CF were negatively correlated with parent reported medication adherence.[296] Compared to non-CF peers, friendship with CF peers were less common and of lower quality,[296] which may be due to strict infection control and clinical segregation policies [124] discouraging in-person contact among people with CF.

Qualitative studies among adolescents and younger adults with CF found a strong sense of stigma or embarrassment with using treatments in the presence of peers.[251, 252] The desire to be seen as healthy or "normal" meant that adolescents with CF were reluctant to bring treatments to friends' homes or to school, which may limit the opportunities for using treatments.[252]

3.3.14 Relationships with the CF care team

Healthcare for people with CF are almost exclusively delivered by multidisciplinary teams (MDT) through specialist CF centres,[124] which meant that the MDT is a core element that plays an important role in the lives of people with CF. A small study among 27 adults with CF failed to detect an association between relationship with the care team and self-reported medication adherence, although it did find that better relationship with care team was associated with better social adjustment.[276]

Qualitative studies have emphasised the importance of CF care teams. Developing a trusting relationship with the team and CF physicians discussing adherence frankly are considered to be important facilitators of adherence for adolescents with CF.[252] CF care teams should also provide “tools” to support adherence, and be creative in identifying and solving potential barriers to adherence.[252] Adults with CF felt that support from care teams are “essential for adherence to therapy”,[259] and that attending CF clinic is an motivator to increase treatment adherence.[251]

As such, CF clinic may provide a structure to systematically evaluate and support adherence with preventative inhaled therapies. A survey in 2008 among specialist CF centres in the US found that 64% of the CF centres reported discussing adherence at every clinic visit, but only 8% of the centres have access to MPR adherence data (EDC was not routinely available in the US during that period).[297] Some centres were concerned that objective adherence data would be used punitively to “catch” people with CF lying about their adherence.[297] Around 20% of the centres felt that adherence would only be a concern if lung function was unstable or if a person with CF was unwell.[297] This emphasises the importance of changing the care team in order to facilitate better treatment adherence among people with CF.[298]

Ten specialist CF centres in the US participated in a quality improvement initiative to regularly assess and address adherence issues in clinics.[299] At the end of the 1-year period, 72% of care staff at those CF centres reported that adherence was being asked during every visit and 100% of staff reported that adherence is important for all patients; which improved from figures of 61% and 89% respectively at the start of the initiative.[299] However, no adherence data (or even outcome data) was systematically collected.[299] Therefore it is uncertain whether this initiative actually improves the adherence levels of people with CF.

3.3.15 Conclusions

Factors that mediate nebuliser adherence among adults with CF are poorly understood. Most studies of adherence determinants among people with CF have eschewed explicit psychological theory, focusing instead on the practical barriers and facilitators to adherence. While these factors may have some explanatory value for low adherence, most of the effects were small and a significant amount of variance in adherence remained unexplained. Many quantitative studies also

found conflicting results, perhaps due to differences in study designs and adherence was measured with error either by self-report or MPR (gold standard EDC adherence data were rarely used). For example, a quantitative study using MPR data found that adherence was negatively correlated with the number of reported barriers,[254] but another quantitative study found that younger adults with CF who reported higher adherence also reported more barriers (perhaps due to people being more aware of the barriers they faced if they persisted with using medications).[253]

A study found that treatment beliefs mediate the relationship between depressive symptoms and treatment adherence,[290] which highlights the importance of studying the role of psychological factors as adherence determinants. Where explicit psychological theory was used in previous studies of potential adherence determinants in CF, only relatively 'narrow' theories have been applied, e.g. the Health Belief Model (which posits that perceived susceptibility to recurrent ill health would be associated with taking the recommended health actions to reduce that susceptibility, e.g. by increasing medication adherence [300]) [274, 275] or the Necessity-Concerns Framework (which posits that patients implicitly weigh the advantages and disadvantages of using treatment uses against the disadvantages when deciding whether or not to adhere to treatments [301]).[259, 277, 278] These theories assume that adherence or non-adherence arises only from rational deliberation.

Yet, dual process theories propose that behaviour may be directed either via conscious reflective deliberation, or through more rapid automatic processing.[302-304] The Capability, Opportunity and Motivation (COM-B) model, which incorporates all potential determinants of action,[305] posits three factors necessary for any behaviour to occur: perceptions of capability, opportunity and motivation. Each of these may be subdivided: capability may be psychological (e.g. knowledge) or physical (e.g. dexterity); opportunity may be social (e.g. permission to use nebulisers at the workplace) or physical (e.g. availability of medication) and motivation may be reflective and deliberative (e.g. necessity, concerns) or non-reflective, drawing on automatic processes (e.g. habit associations).

The COM-B model demands explanations for low adherence over and above treatment or health beliefs, which are one component of reflective motivation. Recent work in other subject areas has highlighted the importance of targeting automatic processes (e.g. habit) for behaviour change in general [306, 307] and to improve medication adherence in other long-term conditions.[7-11, 249] Habit may well be important in sustaining medication adherence among adults with CF, but the literature search found no studies looking at habit in the context of CF medication adherence. As the first step to explore the potential role of habit in nebuliser adherence among adults with CF, the current literature pertaining to habit is reviewed in the next section (Section 3.4).

Chapter 3, Section 4: The concept of ‘habit’ and methods to measure ‘habit’

For some health behaviours, a single action may be adequate to attain desired health outcomes, e.g. a single vaccination.[308] For many other health behaviours, behaviour change must be lasting for health benefits to be realised e.g. the use of CF preventative inhaled therapies – using a single dose of dornase alfa, for example, has negligible health impact.[309]

Various systematic reviews have highlighted the difficulty of changing behaviour, but maintaining behaviour change is even more difficult.[193, 249, 310, 311] A potential mechanism for sustaining behaviour change is habit formation. Drawing heavily on a recent habit scoping review,[250] this section focuses on the concept of habit to understand its role in influencing health-related behaviours and methods to measure habit.

3.4.1 The concept of ‘habit’

3.4.1.1 What is ‘habit’?

Various definitions of ‘habit’ have been used. A definition of ‘habit’ which is coherent and provides evidence-based explanatory mechanism for habitual (health) behaviours is “*a process by which a stimulus automatically generates an impulse towards enacting a behaviour*”.[250]

This definition distinguishes between habit as a process, and habitual behaviour as a manifestation of that process. This definition also incorporates all the characteristics of habit as described in Sections 3.4.1.2 and 3.4.1.3 which distinguishes habitual behaviour from other forms of automatic behaviour. By clarifying that habit activates an impulse towards behaviour instead of activating a behaviour, this definition allows for the possibility that a habit impulse may not always be enacted as a behaviour (see Section 3.4.1.6).

3.4.1.2 Habit is automatic and cue-contingent

Habit is a non-conscious (i.e. automatic) process by which behaviour is contextually cued. For example, an adult with CF may automatically use his nebuliser (behaviour) after walking his dog every morning (contextual cue).[16]

It follows that if the cue is rarely encountered, it is possible for a “strongly habitual” behaviour to be infrequent.[250] For example, if an adult with CF who automatically uses his nebuliser after walking his dog only walks his dog once a week, the adult with CF may also only activate his habit impulse for using nebulisers once a week.

Discontinuation of cue exposure may disrupt habitual behaviour.[312, 313] However, sustained behaviour change may not be achieved just with discontinuation of cue exposure if a return to the ‘previous context’ spontaneously activates unwanted ‘implicit habit’.[250] For example, a person with CF may consistently use his nebuliser after his evening meals whilst in hospital. However, when he returned to his home environment, he might also return to his previous behaviour of spending most of his time after his evening meals playing games on his Xbox console instead.

'Implicit habit' i.e. stored cue-behaviour association may explain why behaviour change interventions typically only have short-term effects [193, 310] in that old behaviours re-emerge after the active intervention period.[250]

3.4.1.3 Habit is acquired by context-dependent repetition

Habit forms through associative learning when a specific behaviour is consistently repeated in a specific setting.[250] This context-dependent repetition gradually shifts the cognitive control of a behaviour from reflective to automatic processes, such that encountering a context is sufficient to elicit the associated behaviour.[250]

A behaviour can also be repeated in different settings (e.g. using nebulisers at different times of the day instead of always after the evening meals). This may help to stave off boredom but in theory, will not contribute to strengthening of habit.[314]

3.4.1.4 Habit determines behaviour frequency – how habit maintains a focal behaviour

The gradual shifting of a behaviour's cognitive control from reflective to automatic processes means that as habit develops, it can cue further context-dependent repetitions which in turn further strengthens the habit.[250] This positive feedback loop means that enacting the behaviour gets progressively easier, even though the initial process of habit formation is effortful.[314]

Automatic control of habitual behaviours reduces the dependence of habitual behaviour on conscious attention or deliberative processes.[250] Habitual behaviour should therefore persist even if attention or conscious motivation wane i.e. habit can shield new behaviours from relapse.[314] In contrast, behaviour which relies on effortful self-regulation (which is a limited mental resource [315-317]) would be susceptible to disruption when self-regulation is reduced during times of stress, or if there is a need to devote resources to other cognitively effortful tasks.[250]

Habit should over-ride intention where opposing habits and intentions (i.e. motives) are present.[250] This is because the impulsive pathway should generate a response more instantaneously than the deliberative pathway. Various moderation tests have demonstrated that intention becomes less predictive of a behaviour as habit strength increases.[250] That means if a person intended to use his nebuliser after his evening meals but he also has a very strong habit of playing games on his Xbox console after his evening meals, it is more likely that the person ended up playing games on his Xbox console. However, findings of moderation tests were not always consistent, e.g. some studies found no interaction [318] whilst other studies even found that intention were *more* predictive of behaviour with stronger habits.[319] The inconsistent findings may be related to differences in study designs and habit measures rather than a genuine lack of moderating impact of habit on the intention-behaviour relationship.[250, 320]

Habit may also narrow people's attention towards the habitual option and reduce accessibility to alternative options. A study found that people with strong habit towards choosing a particular travel mode showed a lack of interest in acquiring new information for other travel options and used less

information in their decision-making.[321] Another study found that people with strong routines tended to use information in a way that is biased towards maintaining their routines.[322] For example, people with strong routines were more likely to be only searching for confirmatory information and preferred to maintain a routine even when presented with contradicting evidence, compared to people with weaker routines.[322]

3.4.1.5 Other potential cognitive benefits of habit

As a behaviour becomes cognitively efficient, self-regulatory resources can be freed up for other tasks. A study asking participants to provide hourly reports of their on-going experience found that people tend to be able to think about things other than the focal behaviour when they are performing that focal behaviour habitually.[323]

Another study used multiple-step mediation analyses to investigate the inter-relation between exercise and healthy nutrition.[324] This study demonstrated that high behaviour-specific (regular exercise) habit strength may facilitate the regulation of another related behaviour (healthy nutrition) with two different ‘mechanisms’.[324] First, as enacting a behaviour becomes more automatic, efficient and effortless with increasing habit strength, previous self-regulatory resources occupied by exercise-specific demand could be invested in the planning of one’s diet.[324] Second, the psychological resources used to master a behaviour can also be ‘transferred’ to facilitate the mastery of another related behaviour, i.e. cognitive transfer.[324]

The potential for habit formation in a single behaviour to facilitate engagement in another health behaviour is particularly pertinent in CF because CF is a multi-system condition requiring multiple treatment types (see Section 2.3).

3.4.1.6 Habit impulse can be inhibited

As discussed in Section 3.4.1.4, habit strength should correlate with likelihood of behavioural enactment. However, habitual behaviour is not an automatic consequence of encountering relevant cues.[250] There is empirical evidence that contextually cued automatic behaviours can be consciously inhibited with sufficient will-power and self-regulatory resources e.g. through vigilant monitoring of cues and behaviour, or planning alternative responses to cues.[250] A study using episode-sampling diaries found a modest level of level of success (self-reported mean success score of 3.57 on a 7-point scale) at inhibiting unwanted habitual behaviour by vigilantly monitoring for a response to cues and inhibiting its performance.[325] Other strategies e.g. distraction or cue avoidance were unsuccessful in that study.[325]

Nonetheless, strategies to tackle unwanted habitual behaviours can be divided into two broad (but potentially overlapping) categories: (1) altering the environment to constrain the behaviour and discontinue cue exposure (since habit is cue-contingent; see Section 3.4.1.2) (2) disrupt the cue-response process e.g. by developing interventions to inhibit habit impulse.[307]

3.4.1.7 *Habitual behaviours may be habitually instigated or habitually executed*

Questions have been raised as to whether complex health behaviours can be habitual, since it is unlikely for complex behaviours to be completely undertaken without conscious mediation.[326] Some of the most compelling studies on 'habit' are based on automation of simple actions e.g. pulling levers, with the assumption that these simple actions transpose to more complex behaviours (i.e. complex habitual actions are viewed as concatenated sequences of simpler and lower-order habitual actions).[250] There is no empirical data supporting this assumption [250] and recent experimental work also highlighted the difficulty of inducing inflexible habits in human subjects.[327]

Action-phase models deconstruct a higher-order behaviour into sequential subcomponents starting prior to action selection and concluding in action completion, e.g. a 'bicycle commute' can be broken down into 'retrieving the bicycle from the garage', 'putting on cycle helmet', 'pedalling', 'navigating the traffic' etc. Conceptualising all habitual behaviours as being automatically selected (i.e. the decision to act in action-phase terminology) *and* automatically performed (involving the completion and termination of action) restricts the explanatory value of habit for complex behaviours. A better theoretical understanding of complex habitual health behaviours is obtained by distinguishing habitual behaviours into two types i.e. habitually instigated sequences (action sequence automatically initiated without deliberation) and habitually executed actions (action performed to completion without conscious input); and recognising that habitual instigation does not necessitate habitual execution and vice versa. Habitual instigation would better match everyday experiences of complex behaviour whereas habitual execution would fit with historical perspective of 'habitual behaviours' as chunked automated sequences of lower-order actions.

This distinction is less meaningful for simple behaviours in which the instigation and execution cannot be easily separated e.g. drinking water. However, this distinction has practical implications for complex health behaviours e.g. using nebuliser. If nebuliser use episodes are habitually instigated (e.g. triggered at the same time of day) but non-habitually performed (e.g. executed mindfully in a varying sequence), habit formation should target the automatic selection of the behaviour (i.e. target the "decision process"). If nebuliser use episodes are consciously instigated (e.g. mindfully triggered) but habitually performed (e.g. performed in an automated and unvarying sequence), then habit formation should aim to automate sequential activation of multiple sub-behaviours (i.e. target the "execution process").

There is also emerging empirical evidence to suggest that instigation, rather than execution habits, are more likely to predict the frequency of health behaviours.[328, 329] Given that a hallmark of habit is that habit should predict the enactment of future behaviour,[250] this evidence suggests that distinguishing between instigation and execution habits is likely to be relevant for understanding health behaviours.

3.4.2 Methods of measuring ‘habit’

The recent scoping review on ‘habit’ [250] identified four types of habit measures. This section summarises those four habit measures, highlights a measure for habit impulse described in a commentary to the scoping review,[330] and discusses the general strengths and limitations of different habit measures. Finally, the characteristics of an adequate method to measure the habit of using nebuliser among adults with CF are considered.

3.4.2.1 Habit measure 1 – frequency in context

The ‘Behaviour Frequency × Context Stability’ (BFCS) is the most commonly used frequency in context measure and can be adapted for a range of habitual behaviours. It is the multiplicative product of self-reported behaviour frequency (e.g. ‘how often do you do X?’) and variation in contextual cues (e.g. ‘when you do X, how often is it performed at the same place?’).[331] This is based on the assumption that ‘strong habits’ have been frequently performed in stable contexts, whereas ‘weak habits’ have been performed in unstable contexts or performed less frequently.[320] However, it is uncertain whether the implied compensatory relationship between behaviour frequency and context stability (i.e. frequent behaviour in varying settings is expected to have the same influence on habit strength as infrequent behaviour in unvarying setting) exists.[332]

BFCS typically relies on researcher-generated cues (e.g. location in the example above) to infer context stability, yet any environmental features can cue habit and contextual cues will differ between individuals.[250] A limitation of BFCS that relies on researcher-generated cues is that it only truly “measure habit” if idiosyncratic contextual cues for a person are correctly identified.[250] BFCS could also be based on cues elicited from participants or could even use a general context instead of specific cues (see example in reference [320]). However, the focus on cue (or context) stability meant that BFCS may be assessing the likelihood habit has formed rather than the automaticity with which habitual impulses are being generated.[250]

3.4.2.2 Habit measure 2 – Self-Report Habit Index (SRHI)

SRHI is a self-report scale designed to assess the experience of habit and the strength of underlying cognitive association.[332] It consists of 12 items reflecting on automaticity, behaviour frequency (to capture the experience of repetition) and self-identity.[332, 333]

The SRHI assumes that people can accurately infer that they are unaware of initiating an action by reflecting on the consequences of the action (i.e. the “symptoms” of habit).[332] It does not require an insight into the habit process itself.[332] However, it is argued that people’s recollection of behaviour and experience is unreliable.[334] Studies have suggested that executive processes leading to habitual actions are inaccessible to conscious awareness, hence people may not be able to distinguish between automatic and non-automatic actions.[334] Not all automatic processes are habits, and people may also not be able to distinguish between actions that are habitual and automatic, or non-habitual and automatic (e.g. non learned forms of automaticity).[334] As a result,

people may misattribute a frequent behaviour as “habit” or “automatic”, when in reality the behavioural response actually requires considerable deliberative planning or cognitive effort.[334]

Generic SRHI items (e.g. ‘Behaviour X is something I do without thinking’) neglect cue or context, but references to specific cues or contexts can be easily accommodated within the item (e.g. ‘Behaviour X in Context Y is something I do without thinking’).[332] However, a study that collected both generic and context-specific SRHI scores found similar results with both context-free and context-specific items.[335]

The parsimony and conceptual basis of SRHI have also been questioned.[250, 336] Behaviour frequency SRHI items are likely to illicit responses that covary closely with performance frequency but ignore frequency with which cues are being encountered.[250] The self-identify items are perhaps redundant, since self-identity is not considered a defining feature of habit.[250]

3.4.2.3 Habit measure 3 – Self-Report Behavioural Automaticity Index (SRBAI)

SRBAI is an automaticity subscale of the SRHI and consists of four items.[336] Limitations of SRHI, e.g. the potential lack of reliability in reflecting on non-conscious processes, also apply to SRBAI. Being more parsimonious, SRBAI is likely to be a more practical tool than SRHI in collecting data for multiple behaviours and/or multiple time points.[336]

However, the reduction in the number of items may reduce the reliability of SRBAI compared to SRHI.[332] The validation datasets for SRBAI showed stronger correlation between behaviour and SRHI compared to SRBAI.[336] suggesting that an assessment of behaviour frequency and/or experience of repetition may be crucial to measure habit.[320] For example, experience of repetition may help in discerning habitual from non-habitual forms of automaticity.[250]

3.4.2.4 Habit measure 4 – Association tests

Association tests are designed to directly assess the strength of cue-behaviour associations. Examples include the Implicit Association Test (IAT) and Go / No-go Association Task (GNAT).[337] These tests operate on the basis that habitual responses should be more quickly and frequently recognised in the presence of cues (since the impulsive pathway should generate a response more instantaneously than the deliberative pathway).[250] Association tests are usually administered in a controlled environment (e.g. a quiet room or separate cubicle) using a computer with webpage application or an appropriate software.[338] Participants may be asked to provide the context or cues for a behaviour; or researcher-generated cues and/or researcher-specified context are used for the test. Participants are then assessed with a behaviour recognition task. This usually involve several behaviours presented as words or images on the computer screen in random order (the wording or images can be modified to take in account appropriate cues / context), whereby the participants respond to each behaviour by pressing a ‘yes’ key or a ‘no’ key on the keyboard.[338] Response times are recorded and processed by the software or webpage application. Quicker response times to a presented behaviour (i.e. lower response latencies) are considered to represent stronger impulse for that behaviour (i.e. stronger habits).

Association tests bypass the subjectivity of self-report and purport to clearly distinguish between implicit (i.e. automatic) vs deliberative processes.[337] However, they must be administered in a controlled environment; hence lack real-world applicability and ecological validity.[250] Large number of trials is required to detect subtle differences in the speed of response.[320] External validity is also a concern since other inter-individual and between cohort factors (e.g. age) could influence the reflex to a stimulus.[339]

3.4.2.5 Self-report of 'habit impulse'

Existing self-report habit measures (see Sections 3.4.2.1 to 3.4.2.3) infer habit from the stability of context in which a behaviour is enacted (BFCS) or from experiences of automaticity with enacted behaviour (SRHI and SRBAI). Therefore, these measures are insensitive to habit-generated impulses that are not enacted; and are not able to distinguish between strong and weak habit-generated impulses when a behaviour is not enacted.[330] Measuring habit impulses offers new opportunities to predict, understand and influence health behaviours.[250, 330] For example, detecting presence of latent or inhibited habit impulses may identify people at risk of relapsing into unwanted habitual behaviours during periods of diminished self-regulatory capacity. This is important because behaviour change and habit formation may well involve substituting an old behaviour with a new one.[320] An impulse measure may also allow a more accurate evaluation of intervention techniques designed to inhibit unwanted habit impulses (e.g. to smoke).[330]

The difficulties of perceiving and recollecting automatic processes are described in Section 3.4.2.2, but some habit impulses may be more open to self-report. Impulse is generated outside conscious awareness, but it may rise into consciousness (e.g. experienced as an urge to enact an action) if the impulse is blocked from being translated into action (see example in reference [330]). Self-report measures specific for impulses to smoke when abstinent have been shown to predict relapse.[330] Therefore, generic measures of habit impulse that are *independent of action* could also be useful in other settings. An example of such items based on the format of SRHI might be: 'When in Context Y, I automatically find myself wanting to do Behaviour X'.[330] The example item is still unlikely to distinguish between habitual from non-habitual automatic responses, so more work is needed to develop and validate reliable measure of habit impulse.[330]

3.4.2.6 All existing measures of habit are necessarily imperfect

Unlike behaviours, habit is a process which cannot be directly observed. Existing self-report measures infer habit indirectly as described in Section 3.4.2.5 and rely on recall of subjective experience. Association tests (see Section 3.4.2.4) purport to directly assess the strength of cue-behaviour associations. While these tests bypass the subjectivity of self-report in terms of the cue-behaviour strength, they may still be subjected to the subjectivity of self-report in terms of identifying cues.[332] In addition, the speed of impulse generation and strength of impulse were still being measured indirectly (as speed of response to a primed target). Therefore, all existing habit measures are at best a surrogate measure of the very essence of habit i.e. a process which

generates an impulse towards action (see Section 3.4.1.1). Association tests may be the ‘most proximal’ measure for habit, thus may be considered the most theoretically valid measure (although it has been argued that speed of response in association tests may conflate non-habitual processes e.g. affective forces or familiarity [332]). However, theoretical validity is not the only necessary property for a useful measurement tool.[340, 341]

The issues with habit measurement also apply to measurements of other psychological constructs. Many ‘proven valid’ measurement tools may actually lack validity, and how respondents interpret most questionnaire items (the dominant form of measurement tool within health psychology) is often unknown.[342] There are also problems with self-report even for a behaviour;[184, 186, 187] and it seems unlikely that self-reported psychological constructs would be more reliable than self-reported behaviours.

This is not to say that an imperfect measure cannot be useful. Imperfect measures can still be adequate, especially if potential biases from the imperfect measures are well understood. Progress has been made in understanding the role of habit within health behaviours since the introduction of SRHI and other habit measures;[332] and further work on habit measures could help to extend habit research and application.

3.4.2.7 If all existing measures of habit are imperfect, what are the characteristics of an adequate measure of habit for nebuliser use among adults with CF?

It could be argued that a habit measure for nebuliser use is “adequate” if it shows an adequate degree of validity and reliability in relation to the purpose of measurement.

Validity:

Validity is the extent to which a measure is linked to the construct that the measure is intended to assess.[342] Validity can be content-related (*face validity* i.e. a measure is measuring what it aims to measure; *construct validity* i.e. a measure is related to underlying theoretical concepts) and criteria-related (*concurrent validity* i.e. a measure is related to another similar measure; *predictive validity*; e.g. does the habit measure predict behaviour enactment?).[343]

The main characteristics of habit are automaticity, cue-contingency and cue-stimulus response learned through context-dependent repetition.[250] At a simplistic level, a content-valid nebuliser habit measure should only measure the defining characteristics of habit and not something else (e.g. nebuliser adherence). However, it is also important to note that habit has several other characteristics, such as its cognitive efficiency and prediction of behaviour enactment.

As discussed in Sections 3.4.2.1 to 3.4.2.6, all existing habit measures are able to capture parts of the habit construct but none (not even association tests) are able to reliably capture ‘habit’ without potential conflation with non-habitual processes. This does not invalidate all existing habit measures. “Validity” must be assessed as a continuum instead of a binary outcome; and these limitations may lessen, but do not necessarily nullify, the validity of habit measures.

Thus, all the measures described in Sections 3.4.2.1 to 3.4.2.5 have a degree of validity, but results from these measures should be interpreted in the context of possible limitations. For example, if the purpose of measuring habit is to investigate the moderating influence of habit on intention but such an effect was not detected using a frequency in context measure; it may be because the frequency in context measure failed to detect implicit habit rather than a genuine absence of habit-intention interaction. However, if the purpose of measuring habit is to investigate the relationship between habit and behaviour frequency (i.e. behaviours that are enacted), the inability to account for implicit habit using a frequency in context measure may not bias the results.

Reliability:

Reliability refers to the consistency of a measure.[344] Reliability can be internal (i.e. consistency within a measure, which can be evaluated with omega coefficient [342]) and external (*test-retest* i.e. stability of a test within a person over time; *inter-rater* i.e. consistency between different raters, judges, or observers).[344]

Since association tests bypass the subjectivity of self-report, they may well have better reliability in terms of the measuring cue-behaviour strength if performed in a controlled environment. It is seems unlikely that the association tests can be reliable outside a controlled environment – even within a controlled environment, large number of trials are needed to detect subtle differences in the speed of response.[320]

Thus, if the purpose of measuring habit is to provide corroborating evidence for self-report habit measures in a controlled environment, an association test would be a highly reliable measure. If the purpose of measuring habit is to track how habit of using nebuliser change from childhood to adulthood among people with CF in a real-world setting, an association test is unlikely to be a reliable measure.

In this thesis, nebuliser habit was measured to explore the relationship between a broad range of potential adherence predictors (including habit) and objective nebuliser adherence. A variety of self-report items for the studies in Chapters 5 & 6 was used. SRBAI was used to measure habit in those studies to avoid excessive burden on participants, because SRBAI is more parsimonious compared to other self-reported habit measures.[336] None of the self-report measures used are perfect. However, all of those measures also provide some insights into the constructs that those measures are designed to assess, and using self-report measures for all the different psychological constructs at least provided a consistent approach. Therefore, it could be argued that the SRBAI measure used in this thesis is adequate for the purpose of measurement.

Chapter 3, Section 5: Summary of the gaps in current evidence and the specific objectives of subsequent thesis chapters to address these gaps

Review of the current CF literature revealed that adherence levels among adults with CF are generally low (median adherence 30-50%), reasons for low adherence remain poorly understood and effective adherence interventions are lacking. A recent James Lind Alliance Priority Setting Partnership has identified effective ways to “improve and sustain adherence to treatment” as one of the top 10 research priorities in CF.[258] Thus, further research in this area is timely and important. There are two areas of limitations in the current evidence base, which this thesis aims to address.

First, electronic data capture (EDC) is generally considered the ‘gold standard’ method to capture adherence data,[168] yet EDC data have only been used to explore a limited range of demographic / treatment factors that potentially influence nebuliser adherence among adults with CF. As discussed in Section 3.1.2, the CF community is fortunate in that I-neb® (which is a tamper-proof intelligent nebuliser machine that automatically and accurately logs every time a drug is being nebulised) is available for routine clinical use. Therefore, the objective of Chapter 4 is to use adherence data captured via I-neb® among 126 adults with CF in Sheffield over a 4-year period to systematically explore a wide range of demographic / treatment factors that potentially influence adherence. Prior to the work under-taken in Chapter 4, the largest EDC adherence dataset in CF only consisted of 108 people over a 1-year period.[179, 345]

Second, even after the extended literature review in Section 3.2, there is a paucity of research looking at the relevance of automatic processes in CF medication adherence. Understanding the role of both non-conscious motivation (e.g. habit) and conscious motivation (e.g. intention) in sustaining nebuliser adherence could lead to more effective adherence interventions. Therefore, the objective of Chapter 5 is to use a mixed methods design to explore a wide range of psychological factors that potentially influence adherence. Adherence data were accurately captured via I-neb® in this mixed methods study among 20 Sheffield adults with CF, thus the exploration of psychological factors is grounded upon reliable adherence data. Any single-centre study can be criticised for the lack of generalisability. Therefore, the objective of Chapter 6 is to replicate the findings in Chapter 5 with a secondary quantitative analysis using prospectively collected data during a pilot randomised controlled trial with 64 participants (ACtiF pilot, ISRCTN13076797). Participants in the pilot trial were recruited from the Wolfson CF Centre (Nottingham) and Wessex Adult CF Centre (Southampton); and nebuliser adherence data from the participants were captured via eTrack® (another form of EDC).

CHAPTER 4: AN OBSERVATIONAL STUDY EXPLORING THE RELATIONSHIP BETWEEN CLINICAL FACTORS AND OBJECTIVE NEBULISER ADHERENCE

Chapter 4, Section 1: Introduction

The literature review in Section 3.2 found that electronic data capture (EDC) data have only been used to explore a limited range of demographic / treatment factors that potentially influence adherence. Other than age, the influence of other demographic factors on nebuliser adherence is uncertain. Understanding the association between demographic factors and adherence could potentially allow clinicians to identify the subgroup of adults with CF that are particularly at risk of low adherence. This understanding is also important for case-mix adjustments to enable robust between-centre comparison and benchmarking using adherence data as quality indicator.[346] Understanding the association between treatment factors and adherence could help inform the therapeutic decisions of clinicians to support nebuliser adherence.[347]

This chapter therefore sets out to systematically explore the relationship between objective nebuliser adherence and a range of demographic & treatment factors.

Chapter 4, Section 2: Methods

4.2.1 Design and setting

This is a single-centre retrospective observational study. All adults with CF diagnosed according to the UK CF Trust criteria [348] in Sheffield aged ≥ 16 years and using I-neb[®] as part of their routine treatment were included, except those with lung transplantation or on ivacaftor. Both lung transplantation and ivacaftor have transformative effects on lung health,[349-351] such that their treatment requirements may no longer represent that of a typical adult with CF.[352, 353] This study was approved by the NHS Health Research Authority (IRAS number: 210313).

4.2.2 Data collection and processing

The following clinical data from 01 January 2013 to 31 December 2016 were extracted from paper notes and electronic patient record:

- Age, in years
- Gender at birth (male / female)
- Best %FEV₁, calculated using the Global Lung Function Initiative (GLI) equations [354]) – this is the highest %FEV₁ reading in the calendar year period

- CF related diabetes (CFRD, present / not present) – CFRD was diagnosed by the clinical team on the basis of oral glucose tolerance test and continuous subcutaneous glucose monitoring results, in accordance to the UK CF Trust guideline.[355]
- *P. aeruginosa* status (chronic / intermittent / no) – determined according to the Leeds criteria.[356]
- Socioeconomic deprivation – calculated as Index of Multiple Deprivation (IMD) scores, which were derived from postcodes.[150]
- Pancreatic status (pancreatic insufficient / pancreatic sufficient) – pancreatic insufficiency was diagnosed by the clinical team on the basis of ≥ 2 faecal pancreatic elastase levels $< 200\mu\text{g/g}$ stool, and symptoms consistent with maldigestion and malabsorption, in accordance to the UK CF Trust guideline.[357]
- Genotype ('severe genotype' / not) – determined according to international consensus,[19] which defined 'severe genotype' as homozygous for Class I-III mutations
- Annual total intravenous antibiotic days (in number of days) – data from 01 January 2012 to 31 December 2012 were also collected
- Nebuliser prescription details

Extracted nebuliser prescription data included three aspects.

First, a treatment regimen was considered "suboptimal" if the minimum required treatment definition was not met (e.g. a person with chronic *P. aeruginosa* infection who was only prescribed once daily dornase alfa),[182] and "minimum required treatment prescribed" if the minimum required treatment definition was met. Data related to *P. aeruginosa* status, %FEV₁, pancreatic status, genotype and prior-year intravenous antibiotics were used to determine the minimum required treatment based on a normative definition.[182]

Second, a treatment regimen was considered "short-term" if the intended treatment duration was three months or fewer (this regimen is typically used for *P. aeruginosa* eradication [80, 135, 358]), and "long-term" if the intended treatment duration was longer than three months (this includes eradication treatment for non-tuberculous mycobacteria which is typically two years in duration [359]).

Third, a treatment regimen was considered "alternating" if on-off or continuous alternating nebulised antibiotics regimen was prescribed, and "continuous" for all other treatment regimens.

Nebuliser adherence data were downloaded from I-neb[®]. Adherence was calculated as a percentage of total nebuliser doses taken against the agreed dose between clinicians and adults with CF. This corresponds with the method of quantifying the implementation of a dosing regimen, as outlined by the Ascertaining Barriers to Compliance (ABC) taxonomy for medication adherence.[156-158] Based on this method of quantifying adherence, adherence levels can vary from 0% to >100% (due to potential nebuliser overuse), with higher adherence being more desirable although nebuliser adherence >100% may not be optimum (this may vary with the

medications – hypertonic saline may be beneficial if used more frequently whereas antibiotics may cause toxicity if used substantially more frequently than the prescribed doses).

Data were managed in a Microsoft Excel v.2010 (Microsoft) spreadsheet, and were checked for accuracy and completeness before analysis. Complete data were collected from all included adults – there is no missing data for any variables. Data extracted from paper notes were independently reviewed by two investigators to ensure accuracy.

4.2.3 Data analysis

Data were analysed using SPSS v24 (IBM Corp). Data for 2013-2016 were combined, and mixed-effects modelling (random effect at individual level) was used to account for repeated measures within an individual. Appropriate descriptive statistics were generated, including tabulation of demographic data for adults on I-neb® (included in the study) and adults not on I-neb® (excluded from the study, since no adherence data). P-values <0.05 were considered statistically significant.

4.2.3.1 Analysis of demographic factors

The first part of the analysis involved demographic factors and used annual adherence (in a calendar year) as the unit of analysis. This is because demographic factors e.g. age are relatively stable and accounting for year-on-year changes in these factors is sufficiently granular.

The analyses consisted of two steps with magnitude of adherence used as the dependent continuous variable in linear models. The first step was univariate linear regression using age (≤ 18 years, 19–25 years, 26–34 years, ≥ 35 years), gender (male vs female), %FEV₁ (<40%, 40–69.9%, 70–99.9%, $\geq 100\%$), CF related diabetes (not present vs present), *P. aeruginosa* status (no *P. aeruginosa*, intermittent, chronic) and deprivation status (five quintiles as measured by Index of Multiple Deprivation, IMD, scores which were derived from postcodes [150]) separately as fixed effects.

Age categories used in the analysis were based on previous studies which demonstrated clear U-shape relationship between adherence and age.[5, 200] %FEV₁ categories were based on previous ESCF studies.[360] Previous studies suggest that gender and disease severity (which may be indicated by %FEV₁ and *P. aeruginosa* status) may influence adherence.[209, 273] Socioeconomic deprivation is of interest because studies have demonstrated that people from more deprived areas in the UK and uninsured adults in the US were less likely to receive preventative inhaled therapies.[150, 151] People with CF related diabetes typically have higher treatment burden since they need to incorporate insulin use in their treatment regimens.[355, 361-363] Therefore, it is worth studying whether this increased burden is associated with lower adherence.

The second step of the analysis was to perform multiple regression using demographic factors that were significantly associated with the outcome of interest as fixed effects.

4.2.3.2 Analysis of treatment factors

The second part of the analysis involved treatment (prescription) factors and used weekly adherence as the unit of analysis. This is because nebuliser prescription is more fluid, and can change several times within a year. For example, it is possible for someone to undergo a *P. aeruginosa* eradication course for three months then spend the rest of nine months in the calendar year on “longer-term” treatments.

The analyses of treatment factors involved the same two steps as described in Section 4.2.3.1. The binary treatment factors used as fixed effects were suboptimal treatment (if minimum required treatment definition [182] was not met) vs minimum required treatment prescribed, “short-term” vs “long-term” (>3 months) regimens, and continuous vs alternating regimens (which could be “on-off” nebulised antibiotics or continuous alternating antibiotics).

Adequacy of prescription is of interest because treatment rationalisation and simplification (e.g. by dropping inhaled mucolytics in someone struggling to even use one out of three prescribed nebulisers per day) is often employed as a strategy to improve adherence among people with CF.[364] Yet a study found that changing twice daily colistin to two doses of once daily colistin did not result in sustained improvement of adherence.[176] “Short-term” vs “long-term” regimens are of interest because adherence in long-term conditions tend to decrease over time.[222, 223, 227] A person may cope better with short-term treatment regimens compared to longer-term treatment regimens if he / she relies mostly on conscious self-regulation to maintain nebuliser use, since self-regulation is effortful and uses limited mental resources.[315] Continuous / alternating regimens are of interest because continuous alternating regimens (whereby two or more inhaled antibiotics are alternated) could be an important strategy to improve clinical outcomes especially among people with more severe lung disease.[148, 365] However, continuous alternating regimens are associated with greater treatment complexity and may impact on adherence. Two sequential multiple regressions were performed, each with weekly adherence as the unit of analysis. The first identified treatment factors that were independently associated with nebuliser adherence. The second incorporated relevant demographic factors identified from the analysis described in Section 4.2.3.1.

Chapter 4, Section 3: Results

This analysis included 126 adults (55, 43.7% were females) over a 4-year period. The year-by-year baseline demographic data were summarised in Table 4.1. The Sheffield cohort was relatively young, with a mean age of 27.1 years (95% CI 25.4 to 28.8 years) in 2016. This may partly explain the high %FEV₁ (mean %FEV₁ exceeded 70% for all four years) of the cohort.

Of note, there was consistent year-on-year increase in mean nebuliser adherence from 43.6% (95% CI 37.1% to 50.2%) in 2013 to 55.1% (95% CI 48.5% to 61.7%) in 2016, although the proportion of I-neb[®] users on suboptimal treatment regimen also increased consistently from 22.7% in 2014 to 29.4% in 2016.

Table 4.1: Characteristics of adults with CF included in this analysis for 2013–2016

Year	2013	2014	2015	2016
Excluded				
Lung transplantation, <i>N</i>	6	6	9	7
On ivacaftor, <i>N</i>	7	7	9	13
Not on I-neb [®] , <i>N</i>	77	73	81	84
Included, <i>N</i>	89	97	104	102
<u>Demographics</u>				
Age in years, mean (95% CI)	25.6 (24.1 to 27.2)	26.2 (24.5 to 27.8)	27.2 (25.5 to 28.8)	27.1 (25.4 to 28.8)
≤ 18 years, <i>N</i> (%)	19 (21.3)	17 (17.5)	17 (16.3)	15 (14.7)
19 – 25 years, <i>N</i> (%)	32 (36.0)	33 (34.0)	33 (31.7)	32 (31.4)
26 – 34 years, <i>N</i> (%)	27 (30.3)	32 (33.0)	32 (30.8)	34 (33.3)
≥ 35 years, <i>N</i> (%)	11 (12.4)	15 (15.5)	22 (21.2)	21 (20.6)
Gender				
Male, <i>N</i> (%)	52 (58.4)	58 (59.8)	61 (58.7)	60 (58.8)
Female, <i>N</i> (%)	37 (41.6)	39 (40.2)	43 (41.3)	42 (41.2)
% predicted FEV ₁ , mean (95% CI)	71.9 (67.3 to 76.6)	72.1 (68.0 to 76.2)	72.9 (69.1 to 76.7)	73.2 (69.4 to 76.9)
< 40%, <i>N</i> (%)	7 (7.9)	4 (4.1)	8 (7.7)	6 (5.9)
40 – 69.9%, <i>N</i> (%)	31 (34.8)	37 (38.1)	32 (30.8)	34 (33.3)
70 – 99.9%, <i>N</i> (%)	45 (50.6)	48 (49.5)	58 (55.8)	55 (53.9)
≥ 100%, <i>N</i> (%)	6 (6.7)	8 (8.2)	6 (5.8)	7 (6.9)
Presence of CFRD (CF related diabetes)				
No CFRD, <i>N</i> (%)	66 (74.2)	72 (74.2)	79 (76.0)	70 (68.6)
CFRD present, <i>N</i> (%)	23 (25.8)	25 (25.8)	25 (24.0)	32 (31.4)
<i>P. aeruginosa</i> status				
No <i>P. aeruginosa</i> , <i>N</i> (%)	17 (19.1)	16 (16.5)	28 (26.9)	33 (32.4)
Intermittent <i>P. aeruginosa</i> , <i>N</i> (%)	25 (28.1)	29 (29.9)	25 (24.0)	20 (19.6)
Chronic <i>P. aeruginosa</i> , <i>N</i> (%)	47 (52.8)	52 (53.6)	51 (49.0)	49 (48.0)
Deprivation quintile				
1 i.e. most affluent, <i>N</i> (%)	11 (12.4)	13 (13.4)	15 (14.4)	14 (13.7)
2, <i>N</i> (%)	8 (9.0)	10 (10.3)	10 (9.6)	11 (10.8)
3, <i>N</i> (%)	26 (29.2)	28 (28.9)	29 (27.9)	27 (26.5)
4, <i>N</i> (%)	21 (23.6)	25 (25.8)	26 (25.0)	24 (23.5)
5 i.e. most deprived, <i>N</i> (%)	23 (25.8)	21 (21.6)	24 (23.1)	26 (25.5)
<u>Treatment details</u>				
Adequacy of prescription				
Suboptimal treatment prescribed, <i>N</i> (%)	25 (28.1)	22 (22.7)	28 (26.9)	30 (29.4)
Minimum required treatment prescribed, <i>N</i> (%)	64 (71.9)	75 (77.3)	76 (73.1)	72 (70.6)
Reason of prescription				
Short-term use, <i>N</i> (%)	7 (7.9)	12 (12.4)	13 (12.5)	5 (4.9)
Long-term use, <i>N</i> (%)	82 (92.1)	85 (87.6)	91 (87.5)	97 (95.1)
Nature of prescription				
Continuous regimen, <i>N</i> (%)	60 (67.4)	65 (67.0)	73 (70.2)	79 (77.5)
Alternating regimen, <i>N</i> (%)	29 (32.6)	32 (33.0)	31 (39.8)	23 (22.5)
% adherence, mean (95% CI)	43.6 (37.1 to 50.2)	49.9 (42.9 to 56.9)	53.3 (46.8 to 59.8)	55.1 (48.5 to 61.7)

I-neb[®] is typically reserved for people who require nebulised antibiotics. In comparison to those not on I-neb[®], adults on I-neb[®] had more severe phenotype as evidenced by higher proportions of CF related diabetes and chronic *P. aeruginosa* infection (see Table 4.2). This suggests that older adults (≥35 years) with mild phenotype (thus less likely to be infected by *P. aeruginosa*) are unlikely to require I-neb[®], and clinicians were appropriately targeting the use of I-neb[®] for those

with more severe lung disease. A smaller proportion of adults on I-neb[®] had normal FEV₁ ($\geq 100\%$); but also a smaller proportion had very low FEV₁ ($< 40\%$) since adaptive aerosol delivery device (e.g. an I-neb[®]), which only releases aerosol with an inhalation of sufficient quality,[170] is a struggle to use at such low levels of FEV₁. Males were more likely to use I-neb[®] – for each calendar year, $> 60\%$ of males were on I-neb[®] but $< 50\%$ of females were on I-neb[®]. I-neb[®] use in Sheffield did not differ according to socioeconomic deprivation, even though a recent UK CF registry analysis found that adults from more deprived areas were less likely to be on preventative inhaled therapies.[150]

Table 4.2: Demographic data of adults on I-neb[®] vs adults not on I-neb[®] for 2013–2016

Year	2013		2014		2015		2016	
	On I-neb [®] † N = 89	Not on I-neb [®] ‡ N = 77	On I-neb [®] † N = 97	Not on I-neb [®] ‡ N = 73	On I-neb [®] † N = 104	Not on I-neb [®] ‡ N = 81	On I-neb [®] † N = 102	Not on I-neb [®] ‡ N = 84
Age in years, mean (95% CI)	25.6 (24.1 to 27.2)	27.5 (25.1 to 29.9)	26.2 (24.5 to 27.8)	28.9 (26.4 to 31.3)	27.2 (25.5 to 28.8)	29.5 (27.1 to 31.8)	27.1 (25.4 to 28.8)	30.5 (28.2 to 32.8)
≤ 18 years, N (%)	19 (21.3)	16 (20.8)	17 (17.5)	11 (15.1)	17 (16.3)	10 (12.3)	15 (14.7)	8 (9.5)
19 – 25 years, N (%)	32 (36.0)	27 (35.1)	33 (34.0)	21 (28.8)	33 (31.7)	25 (30.9)	32 (31.4)	27 (32.1)
26 – 34 years, N (%)	27 (30.3)	17 (22.1)	32 (33.0)	24 (32.9)	32 (30.8)	26 (32.1)	34 (33.3)	25 (29.8)
≥ 35 years, N (%)	11 (12.4)	17 (22.1)	15 (15.5)	17 (23.3)	22 (21.2)	20 (24.7)	21 (20.6)	24 (28.6)
Gender								
Male, N (%)	52 (58.4)	38 (49.4)	58 (59.8)	32 (43.8)	61 (58.7)	37 (45.7)	60 (58.8)	36 (42.9)
Female, N (%)	37 (41.6)	39 (50.6)	39 (40.2)	41 (54.2)	43 (41.3)	44 (54.3)	42 (41.2)	48 (57.1)
% predicted FEV ₁ , † mean (95% CI)	71.9 (67.3 to 76.6)	75.0 (68.9 to 81.1)	72.1 (68.0 to 76.2)	72.3 (65.9 to 78.6)	72.9 (69.1 to 76.7)	72.8 (67.3 to 78.4)	73.2 (69.4 to 76.9)	72.5 (67.0 to 78.1)
< 40%, N (%)	7 (7.9)	9 (11.8)	4 (4.1)	12 (16.7)	8 (7.7)	10 (12.5)	6 (5.9)	12 (14.5)
40 – 69.9%, N (%)	31 (34.8)	19 (25.0)	37 (38.1)	17 (23.6)	32 (30.8)	19 (23.8)	34 (33.3)	17 (20.5)
70 – 99.9%, N (%)	45 (50.6)	36 (47.4)	48 (49.5)	35 (48.6)	58 (55.8)	45 (56.3)	55 (53.9)	48 (57.8)
≥ 100%, N (%)	6 (6.7)	12 (15.8)	8 (8.2)	8 (11.1)	6 (5.8)	6 (7.5)	7 (6.9)	6 (7.2)
Presence of CF related diabetes								
No CFRD, N (%)	66 (74.2)	61 (79.2)	72 (74.2)	56 (76.7)	79 (76.0)	64 (79.0)	70 (68.6)	62 (73.8)
CFRD present, N (%)	23 (25.8)	16 (20.8)	25 (25.8)	17 (23.3)	25 (24.0)	17 (21.0)	32 (31.4)	22 (26.2)
<i>P. aeruginosa</i> status								
No <i>P. aeruginosa</i> , N (%)	17 (19.1)	43 (55.8)	16 (16.5)	41 (56.2)	28 (26.9)	46 (56.8)	33 (32.4)	45 (53.6)
Intermittent <i>P. aeruginosa</i> , N (%)	25 (28.1)	12 (15.6)	29 (29.9)	7 (9.6)	25 (24.0)	6 (7.4)	20 (19.6)	9 (10.7)
Chronic <i>P. aeruginosa</i> , N (%)	47 (52.8)	22 (28.6)	52 (53.6)	25 (34.2)	51 (49.0)	29 (35.8)	49 (48.0)	30 (35.7)
Deprivation quintile								
1 i.e. most affluent, N (%)	11 (12.4)	13 (16.9)	13 (13.4)	12 (16.4)	15 (14.4)	13 (16.0)	14 (13.7)	14 (16.7)
2, N (%)	8 (9.0)	7 (9.1)	10 (10.3)	5 (6.8)	10 (9.6)	6 (7.4)	11 (10.8)	11 (13.1)
3, N (%)	26 (29.2)	11 (14.3)	28 (28.9)	12 (16.4)	29 (27.9)	14 (17.3)	27 (26.5)	13 (15.5)
4, N (%)	21 (23.6)	21 (27.3)	25 (25.8)	17 (23.3)	26 (25.0)	18 (22.2)	24 (23.5)	21 (25.0)
5 i.e. most deprived, N (%)	23 (25.8)	25 (32.5)	21 (21.6)	27 (37.0)	24 (23.1)	30 (37.0)	26 (25.5)	25 (29.8)

† Each person “on I-neb[®]” had ≥ 3 months of I-neb[®] adherence data in a calendar year.

‡ A person on I-neb[®] for < 3 months in a calendar year (e.g. I-neb[®] only initiated in Dec ‘16) was considered as “not on I-neb[®]”. A person “not on I-neb[®]” might be using non-chipped nebulisers and/or using dry powder inhalers, or not using any form of preventative inhaled therapies.

¶ One person “not on I-neb[®]” did not provide any %FEV₁ readings from 2013 to 2016 due to the inability to perform spirometry. There is otherwise no missing data.

The analysis for demographic factors using annual adherence as the unit of analysis included 392 observations, whilst the analysis for treatment factors using weekly adherence as the unit of analysis included 18,303 observations. People within the 19–25 years age range tended to have the lowest levels of adherence across all four years (see Table 4.3).

Table 4.3: Magnitude of adherence according to various demographic and treatment factors

Year	2013	2014	2015	2016
	Mean % adherence (95% CI)	Mean % adherence (95% CI)	Mean % adherence (95% CI)	Mean % adherence (95% CI)
Demographic factors	<i>N</i> = 89	<i>N</i> = 97	<i>N</i> = 104	<i>N</i> = 102
Age range [‡]				
≤ 18 years	41.7 (25.9 to 57.5)	52.9 (33.8 to 72.0)	59.3 (40.1 to 78.5)	59.3 (39.0 to 79.7)
19 – 25 years	38.2 (28.2 to 48.2)	40.9 (29.0 to 52.7)	38.7 (28.1 to 49.3)	40.3 (29.2 to 51.5)
26 – 34 years	44.2 (30.5 to 57.8)	53.1 (39.3 to 66.8)	60.5 (47.4 to 73.6)	62.5 (49.7 to 75.2)
≥ 35 years	61.4 (44.1 to 78.6)	59.6 (46.8 to 72.5)	60.0 (48.8 to 71.2)	62.6 (51.4 to 73.8)
Gender				
Male	47.0 (37.9 to 56.1)	53.9 (44.5 to 63.3)	57.1 (47.9 to 66.3)	59.7 (51.0 to 68.4)
Female	38.8 (29.4 to 48.3)	43.9 (33.5 to 54.4)	47.9 (38.9 to 56.8)	48.5 (38.1 to 58.8)
% predicted FEV ₁ [†]				
< 40%	37.1 (10.8 to 63.3)	30.0 (2.1 to 57.8)	61.1 (33.4 to 88.8)	53.6 (13.6 to 93.6)
40 – 69.9%	42.6 (32.8 to 52.7)	54.6 (44.2 to 65.1)	45.7 (35.5 to 55.8)	50.3 (39.9 to 60.8)
70 – 99.9%	45.3 (34.9 to 55.6)	51.6 (41.2 to 61.9)	58.2 (49.0 to 67.4)	59.7 (49.9 to 69.5)
≥ 100%	44.0 (10.4 to 77.6)	28.0 (0 to 63.7)	35.7 (0 to 76.8)	43.1 (20.1 to 66.2)
Presence of CFRD (CF related diabetes)				
No CFRD	43.0 (35.2 to 50.8)	49.3 (40.8 to 57.8)	50.5 (42.8 to 58.3)	50.3 (42.5 to 58.1)
CFRD present	45.4 (32.4 to 58.5)	51.5 (38.8 to 64.3)	61.9 (49.8 to 74.0)	65.6 (53.4 to 77.8)
<i>P. aeruginosa</i> status [†]				
No <i>P. aeruginosa</i>	56.3 (38.0 to 74.6)	51.7 (35.1 to 68.4)	52.6 (38.6 to 66.6)	60.0 (47.0 to 73.0)
Intermittent <i>P. aeruginosa</i>	37.0 (24.5 to 49.4)	46.0 (33.5 to 58.5)	60.1 (45.7 to 74.5)	57.3 (41.2 to 73.4)
Chronic <i>P. aeruginosa</i>	42.6 (34.0 to 51.1)	51.5 (41.2 to 61.8)	50.3 (41.5 to 59.1)	50.9 (41.9 to 59.9)
Deprivation quintile [‡]				
1 i.e. most affluent	65.9 (47.0 to 84.8)	69.9 (56.4 to 83.4)	69.0 (51.6 to 86.4)	72.4 (55.4 to 89.4)
2	34.9 (2.7 to 67.1)	48.4 (20.4 to 76.3)	55.0 (27.5 to 82.5)	46.9 (33.0 to 60.9)
3	43.6 (31.7 to 55.5)	45.5 (33.8 to 57.3)	49.5 (37.1 to 61.9)	58.9 (45.9 to 71.8)
4	40.8 (27.7 to 53.9)	52.0 (35.5 to 68.4)	53.5 (40.8 to 66.1)	53.5 (38.1 to 69.0)
5 i.e. most deprived	38.5 (25.0 to 52.1)	41.6 (25.4 to 57.8)	47.0 (32.0 to 62.0)	46.7 (31.9 to 61.5)
Treatment factors [▼]	<i>4,078 weeks of observations</i>	<i>4,429 weeks of observations</i>	<i>5,022 weeks of observations</i>	<i>4,774 weeks of observations</i>
Adequacy of prescription [§]				
Suboptimal treatment prescribed	31.2 (28.6 to 33.9)	45.5 (42.3 to 48.8)	34.4 (32.4 to 36.4)	38.6 (36.2 to 41.0)
Minimum required treatment prescribed	44.5 (43.2 to 45.8)	47.0 (45.7 to 48.3)	57.3 (56.0 to 58.6)	57.3 (56.0 to 58.6)
Reason of prescription				
Short-term use [¶] (<i>P. aeruginosa</i> eradication)	49.9 (40.8 to 59.0)	58.6 (51.1 to 66.1)	62.6 (55.4 to 69.7)	63.9 (53.3 to 74.4)
Long-term use	41.6 (40.5 to 42.8)	46.3 (45.0 to 47.5)	51.8 (50.6 to 52.9)	52.7 (51.5 to 53.8)
Nature of prescription				
Continuous regimen	38.6 (37.2 to 39.9)	40.2 (38.8 to 41.6)	48.7 (47.4 to 50.0)	49.3 (48.1 to 50.6)
Alternating regimen	50.4 (48.0 to 52.7)	66.3 (63.8 to 68.7)	63.5 (61.1 to 65.9)	70.5 (67.8 to 73.1)

[‡] The age categories were based previous studies which demonstrated a U-shaped relationship between adherence and age [5, 200]

[†] The %FEV₁ categories were based on previous ESCF studies [360]

[†] *P. aeruginosa* status was determined using the Leeds criteria [356]

[‡] The deprivation quintile was measured as Index of Multiple Deprivation (IMD) scores, which were derived from postcodes [150]

[▼] The unit of analysis for treatment factor was weekly adherence. Therefore, the year-by-year descriptive data for adherence stratified according to treatment factors did not account for correlated data from repeated measures within an individual.

[§] Minimum required treatment according to clinical characteristics was determined based on a previously published normative definition.[182] Treatment was considered “suboptimal” if the minimum required treatment definition was not met for that week, e.g. a person with chronic *P. aeruginosa* infection who was only prescribed once daily dornase alfa.

[¶] A treatment regimen was considered “short-term” if treatment duration for that course of treatment was ≤3 months (this is typically used for *P. aeruginosa* eradication). Eradication treatment for non-tuberculous mycobacteria (NTM) is typically two years in duration and is therefore considered “long-term use”.

Adults without *P. aeruginosa* and those in the most affluent quintile also tended to have higher adherence. However, increase in adherence from 2013 to 2016 were similar for each deprivation quintile (~10% absolute increase in adherence), suggesting that deprivation status did not influence the likelihood for improvement in adherence. There were no clear differences in adherence levels among those with or without CF related diabetes, and for different categories of %FEV₁. Shorter-term treatments (for *P. aeruginosa* eradication), alternating regimens and prescriptions that met the minimum requirements of adequacy according clinical characteristics were associated with higher adherence. However the descriptive results for treatment factors should be interpreted with caution because the year-by-year descriptive data did not account for the correlation from repeated weekly measures within an individual.

4.3.1 Results for demographic factors

People aged 19–25 years had the lowest adherence whilst people aged ≥35 years had the highest adherence (see Table 4.4).

Table 4.4: Summary of results from mixed-effects linear regression models (random effect at individual level, to account for repeated measures within an individual) for demographic factors

Variable	Magnitude of adherence	
	Regression coefficient ^Δ (95% CI)	P-value
<u>Univariate analysis:</u>		
Age range^Φ (≥ 35 years as reference)		< 0.001
≤ 18 years	–22.0 (–34.2 to –9.8)	< 0.001
19 – 25 years	–26.3 (–37.4 to –15.3)	< 0.001
26 – 34 years	–17.9 (–28.0 to –7.7)	0.001
Female	–9.7 (–20.7 to 1.3)	0.083
% predicted FEV ₁ [¶] (≥ 100% as reference)		0.640
< 40%	5.1 (–12.2 to 22.4)	0.564
40 – 69.9%	4.6 (–9.5 to 18.8)	0.520
70 – 99.9%	7.4 (–5.3 to 20.1)	0.251
CF related diabetes present	7.6 (–2.4 to 17.5)	0.135
<i>P. aeruginosa</i> status [†] (No <i>P. aeruginosa</i> as reference)		0.055
Intermittent <i>P. aeruginosa</i>	–4.4 (–10.9 to 2.1)	0.180
Chronic <i>P. aeruginosa</i>	–10.3 (–18.6 to –1.9)	0.016
Deprivation quintile [‡] (5 i.e. most deprived as reference)		0.231
1 i.e. most affluent	11.2 (–4.8 to 27.1)	0.170
2	–8.1 (–23.2 to 7.0)	0.292
3	0.7 (–11.8 to 13.3)	0.911
4	5.4 (–7.0 to 17.8)	0.396
<u>Multivariate analysis, model 1:</u>		
Age range^Φ (≥ 35 years as reference)		< 0.001
≤ 18 years	–25.3 (–37.8 to –12.9)	< 0.001
19 – 25 years	–28.5 (–39.6 to –17.4)	< 0.001
26 – 34 years	–18.7 (–28.8 to –8.7)	< 0.001
Female [◇]	–8.1 (–19.0 to 2.8)	0.145
<i>P. aeruginosa</i> status[†] (No <i>P. aeruginosa</i> as reference)		0.006
Intermittent <i>P. aeruginosa</i>	–4.5 (–10.8 to 1.8)	0.157
Chronic <i>P. aeruginosa</i>	–13.5 (–21.8 to –5.2)	0.002

^Δ A coefficient of 1.0 in these analyses indicates an absolute increase of adherence by 1.0% (magnitude of adherence can vary from 0 to >100%, with higher adherence being more desirable).

^Φ The age categories were based previous studies which demonstrated a U-shaped relationship between adherence and age [5, 200]

[¶] The %FEV₁ categories were based on previous ESCF studies [360]

[†] *P. aeruginosa* status was determined using the Leeds criteria [356]

[‡] The deprivation quintile was measured as Index of Multiple Deprivation (IMD) scores, which were derived from postcodes [150]

[◇] Gender was included in the multivariate model although the p-value did not reach statistical significance in the univariate analysis because gender had a substantial effect on adherence. The results of multivariate analysis were similar with or without gender as a covariate.

Compared to people aged ≥ 35 years, adherence levels of people aged 19–25 years were on average 28.5% lower (95% CI 17.4% to 39.6%) after accounting for *P. aeruginosa* status and gender. *P. aeruginosa* status was also independently associated with adherence – people without *P. aeruginosa* tended to have the highest adherence levels whilst people with chronic *P. aeruginosa* infection tended to have the lowest adherence levels.

Interestingly, there was no significant differences in adherence according to deprivation quintiles. Even by analysing deprivation as a binary variable (most affluent quintile vs others), the difference in adherence was still not statistically significant, with mean coefficient of 10.3% (95% CI –3.7% to 24.3%), p-value 0.150.

4.3.2 Results for treatment factors

Most people were on long-term continuous treatments that met the minimum requirements for adequacy according to clinical characteristics. Among the 18,303 weeks of adherence data used for analysis; 3,898 weeks were suboptimal treatments given a person's clinical characteristics (among 52 people), 4,181 weeks were alternating treatment regimens (among 49 people, eight of whom were on “on / off” regimens), and 469 weeks were eradication treatments (among 27 people, four of whom had >1 course of *P. aeruginosa* eradication).

There was no difference between alternating (the vast majority were continuous alternating regimens whereby one nebulised antibiotic was alternated with another nebulised antibiotic, instead of “on / off” regimens whereby periods on one nebulised antibiotic was alternated with periods without inhaled antibiotics) vs continuous treatment regimens (see Table 4.5). Compared to longer-term regimens, shorter-term treatments (typically used for *P. aeruginosa* eradication) were associated with an average of 12.4% higher adherence (95% CI 9.5% to 15.3%).

Inadequate prescriptions (e.g. prescribing only one dose of inhaled mucolytics instead of three doses of treatments per day for someone with chronic *P. aeruginosa* infection) may result in “higher adherence”. However, the apparent adherence increase of only 4% to 8% was modest in comparison to the reduction in denominator by a third or two-thirds.

Both age and *P. aeruginosa* status remained as independent predictors of adherence in the multiple regression model using weekly adherence as the unit of analysis, which included relevant demographic and treatment factors (see Table 4.5, multivariate analysis Model 2). This suggests that the potential influence of age and *P. aeruginosa* status on adherence cannot simply be explained by older adults with milder phenotypes (thus less likely to be infected by *P. aeruginosa*) being prescribed less complex treatment regimens. This also suggests that similar results would be obtained in Section 4.3.1 if weekly adherence, instead of annual adherence, was used as the unit of analysis.

Table 4.5: Summary of results from mixed-effects linear regression models (random effect at individual level, to account for repeated measures within an individual) for treatment factors with % adherence per week as the dependent variable

	Magnitude of adherence	
	Regression coefficient ^Δ (95% CI)	P-value
<u>Univariate analysis:</u>		
Minimum required treatment prescribed[§]	−5.1 (−6.7 to −3.5)	< 0.001
Short-term use[¶] (<i>P. aeruginosa</i> eradication)	12.0 (9.1 to 14.9)	< 0.001
Alternating regimen	−0.3 (−2.1 to 1.4)	0.713
<u>Multivariate analysis, model 1:</u>		
Minimum required treatment prescribed[§]	−5.4 (−7.0 to −3.8)	< 0.001
Short-term use[¶] (<i>P. aeruginosa</i> eradication)	12.4 (9.5 to 15.3)	< 0.001
<u>Multivariate analysis, model 2:</u>		
Minimum required treatment prescribed[§]	−6.1 (−7.7 to −4.5)	< 0.001
Short-term use[¶] (<i>P. aeruginosa</i> eradication)	14.9 (12.0 to 17.8)	< 0.001
Age range[‡] (≥ 35 years as reference)		< 0.001
≤ 18 years	−37.4 (−41.8 to −33.1)	< 0.001
19 – 25 years	−37.2 (−41.0 to −33.3)	< 0.001
26 – 34 years	−26.8 (−30.1 to −23.4)	< 0.001
<i>P. aeruginosa</i> status[†] (No <i>P. aeruginosa</i> as reference)		< 0.001
Intermittent <i>P. aeruginosa</i>	−7.4 (−9.3 to −5.6)	< 0.001
Chronic <i>P. aeruginosa</i>	−16.4 (−19.0 to −13.7)	< 0.001

^Δ A coefficient of 1.0 in these analyses indicates an absolute increase of adherence by 1.0% (magnitude of adherence can vary from 0 to >100%, with higher adherence being more desirable).

[§] Minimum required treatment according to clinical characteristics was determined based on previously published normative definition.[182] Treatment was considered “suboptimal” if the minimum required treatment definition was not met for that week, e.g. a person with chronic *P. aeruginosa* infection who was only prescribed once daily dornase alfa.

[¶] A treatment regimen was considered “short-term” if treatment duration for that course of treatment was ≤3 months (this is typically used for *P. aeruginosa* eradication). Eradication treatment for non-tuberculous mycobacteria (NTM) is typically two years in duration and is therefore considered “long-term use”.

[‡] The age categories were based previous studies which demonstrated a U-shaped relationship between adherence and age [5, 200]

[†] *P. aeruginosa* status was determined using the Leeds criteria [356]

Chapter 4, Section 4: Discussion

4.4.1 Why is the U-shape relationship between adherence and age relevant for CF clinical care?

This study found a U-shape relationship between adherence and age (lowest adherence among people aged 19–25 years), even after accounting for various other demographic and treatment factors. This finding is in keeping with previous studies.[200, 283]

This finding may partly explain why %FEV₁ decline in CF is most pronounced during adolescence and young adulthood,[205, 366-368] although this is the age range when most people without CF actually reach their peak physical health.[369] There have been various quality improvement initiatives targeting the transition care arrangement of adolescents with CF.[370-375] Perhaps there is also a need to pay particular attention to the adherence of younger adults with CF, although adherence is important for everyone.

4.4.2 Is the association between adherence and *P. aeruginosa* status genuine, or merely an artefact of the method to define *P. aeruginosa* status?

This study also found an association between adherence and *P. aeruginosa* status defined according to the Leeds criteria, which may indicate severity of lung disease. However, this result does not necessarily imply that disease severity influences adherence levels among adults with CF. Indeed, there was no association between adherence and %FEV₁, which is generally considered the most important indicator for lung disease severity among people with CF.[205-208].

The association between adherence and *P. aeruginosa* status in this study should be interpreted in light of the Leeds criteria's potential limitations in defining *P. aeruginosa* status among adults with CF. The Leeds criteria is the most commonly used definition for *P. aeruginosa* status in CF epidemiology research.[356, 376] However, these criteria were developed in a paediatric population and there is emerging evidence to suggest that the Leeds criteria work less well among adults with CF.[377, 378] The Leeds criteria are based solely on the proportion of positive respiratory cultures [356] – recent studies using polymerase chain reaction (PCR) techniques have shown that the Leeds criteria are insensitive with a tendency to under-diagnose chronic *P. aeruginosa* as intermittent infection.[379, 380] Higher nebuliser adherence would be expected to suppress growth of *P. aeruginosa*,[378] hence it may be that people who did not culture *P. aeruginosa* in their respiratory samples (i.e. fulfilled the Leeds criteria for no *P. aeruginosa*) simply have higher adherence; instead of disease severity as indicated by *P. aeruginosa* status genuinely impacted on adherence levels.

Therefore, this finding emphasises the need for a better definition of *P. aeruginosa* status among adults with CF. *P. aeruginosa* status drives the decision to initiate inhaled antibiotics among adults with CF [123, 358] and inadequate prescription of efficacious treatment (“therapeutic inertia”) is the second biggest cause of treatment under-utilisation after low adherence.[153, 154] If the diagnosis of chronic *P. aeruginosa* infection were inadvertently missed among people with high adherence simply because their respiratory samples were less likely to be culture positive, their inhaled antibiotics may be inappropriately stopped with negative consequences on their lung health. There is perhaps a role for using formal consensus methods (e.g. nominal group technique or Delphi method [381]) in order to explicitly develop a pragmatic definition of chronic *P. aeruginosa* infection among adults with CF that moves beyond solely depending on standard microbiological results.

4.4.3 What is the impact of treatment duration on adherence, and why is this relevant for CF care?

In keeping with studies in other subject areas,[222, 223, 227] this study found that adherence to shorter-term treatments (for *P. aeruginosa* eradication) tended to be higher than adherence to longer-term treatments. Adherence between *P. aeruginosa* eradication and longer-term treatments

among people with CF had not been directly compared in the past. On one hand, this finding is reassuring in that adherence to eradication therapy could be higher than typical adherence levels to long-term therapies by 12% to 18%. *P. aeruginosa* eradication therapy have been shown to mitigate %FEV₁ decline and delay onset of chronic infection,[358] hence high adherence to these therapies would be expected to have substantial long-term health benefits for people with CF. On the other hand, this finding emphasises the challenge of maintaining long-term adherence to preventative inhaled therapies among adults with CF.

A potential explanation for higher adherence with shorter-term treatments is that people were able to summon adequate self-regulation and focus their attention on nebuliser use over a relatively brief period of time. Both self-regulation and attention are limited mental resources.[315] A potential response to limited resources is conservation,[315, 382] i.e. less effort is exerted in using nebuliser to sustain adherence over longer periods or to cope with other CF treatments. Thus, a potential 'cost' of relying on effortful self-regulation is suboptimal adherence. Qualitative studies have described the difficult trade-offs between using treatments and other life goals (e.g. people choosing to skip treatment every few days or when feeling well).[251, 252, 259]

It is therefore worthwhile to explore the role of habit in the health behaviour of using nebuliser among adults with CF – this is the objective of the studies reported in Chapters 5 & 6. If habit can sustain nebuliser adherence, it may be possible to instigate nebuliser use automatically in the presence of environment cues, thus by-passing the cognitive effort in deciding whether to instigate nebuliser use or to pursue other activities.[250, 314]

4.4.4 Treatment rationalisation (i.e. reducing the number of prescribed doses) is a common strategy to support adherence in CF, but is it actually associated with more effective adherence?

Another finding of this study is that treatment rationalisation by reducing the number of prescribed nebulisers was only associated with modest increase in adherence by 4% to 8%. An example of treatment rationalisation is to reduce the agreed prescription from three nebuliser doses per day (i.e. twice daily antibiotics and once daily mucolytic) to just two nebuliser doses a per day (i.e. only twice daily antibiotics). If the number of nebuliser doses used remained the same, such a decrease in agreed prescription would be expected to increase adherence by 33% (e.g. from 67% to 100% if a person continued to use two nebulisers per day and the agreed prescription was reduced from three doses per day to two doses per day).

Percentage adherence depends both on the numerator (i.e. the actual number of doses taken) and denominator (i.e. the target number of doses to be taken). The observed higher percentage adherence among adults on suboptimal prescriptions might be intuitively interpreted as more effective use of preventative inhaled therapy (i.e. an increase in the numerator). However, it is likely that the increase in percentage is simply driven by a decrease in denominator (i.e. decrease

in the target number of doses to be taken each day). Therefore, the observed higher percentage adherence among adults on suboptimal prescriptions may counter-intuitively represent a decrease in the effectiveness of preventative inhaled therapy. This then raises the question as to whether the current methods of quantifying the implementation phase of adherence is adequate to reflect effective medication use among people with CF.

According to the ABC taxonomy for medication adherence, in operationalising the implementation of a treatment regimen, “clinically relevant definitions need to be developed, indicating which deviation from the prescribed medication regimen is sufficient to influence adversely the regimen’s intended effect”.[156] Focusing on inhaled therapies for asthma and COPD, the Respiratory Effectiveness Group has suggested that successful mastery of the inhaler-specific technique should be incorporated in adherence quantification to consider “successful medication adherence in a holistic way” because inhaler technique errors would result in failure to receive prescribed medications.[383] In other words, trying but failing to use an inhaler correctly should be reflected as an “implementation failure”.

However, even with perfect technique, efficacious medications that are required but are not prescribed could never be successfully implemented by an adult with CF. In general, inadequate prescription of efficacious treatment (“therapeutic inertia”) is the second biggest cause of treatment under-utilisation after low adherence.[153, 154] Therapeutic inertia is a particular problem in CF because “treatment burden” is widely perceived to be an insurmountable barrier to adherence,[6] treatment rationalisation is often employed as a strategy to support adherence,[364] yet treatment rationalisation will involve dropping efficacious treatment(s) from an agreed prescription and hence reduce the effectiveness of a treatment regimen. At least in other respiratory conditions e.g. asthma or COPD, there is the option of using combination inhalers such that treatment rationalisation merely involve switching devices without necessarily reducing the effectiveness of a treatment regimen (e.g. Trelegy[®] Ellipta inhaler contains an inhaled corticosteroid, a long-acting muscarinic antagonist and long-acting β_2 -agonist, thus allows triple therapy to be delivered with a single puff once daily [384]).

Empirical evidence suggests that therapeutic inertia is a large scale problem in CF. There remains substantial variation in the prescription of inhaled treatments,[149-151] and recent research showed that only around two-thirds of people with CF were prescribed the recommended preventative inhaled therapies.[149, 152] This study showed that at some point during each calendar year between 2013 and 2016, 22–29% of the adults using I-neb[®] in Sheffield were on suboptimal treatment regimen based on a normative definition using targets derived from consensus guidelines that are informed by randomised control trials.[182] Although this study found a consistent year-on-year increase in mean nebuliser adherence among Sheffield adults from 43.6% (95% CI 37.1% to 50.2%) in 2013 to 55.1% (95% CI 48.5% to 61.7%) in 2016 and there is a trend of improving adherence even after stratification according to age categories (i.e.

adherence increase is not merely a function of ageing population), it is still uncertain whether “effective adherence” has actually improved over the 4-year period. Since the proportions of adults with suboptimal treatment regimen have also increased from 2014 to 2016, the apparent adherence improvement may simply be an artefact of treatment rationalisation. After all, the only other adherence dataset which spanned over two years showed static adherence levels in a CF centre over a 5-year period,[177] and there are no effective interventions to support adherence in routine clinical practice. These examples add to the argument that perhaps there is a need to quantify CF “adherence” in a way that reflects effectiveness of a treatment regimen, by taking into account a person’s clinical characteristics in defining the minimum required treatment. Such a method of quantifying adherence may allow the actual impact of “treatment rationalisation” among people with CF to be better understood, and could potentially guide prescribing decisions.

4.4.5 Is a more complex treatment regimen associated with lower adherence?

Previous observational studies found that adherence tended to increase with higher numbers of prescribed medications (i.e. increasing regimen complexity) [283] and that adherence levels were similar regardless of number of prescribed nebuliser doses.[116, 176] This study found that alternating regimens (usually more complex than continuous regimens because the vast majority of these consisted of continuous alternating regimens which involved alternating between different nebulised antibiotics at fixed time intervals) and continuous regimens tended to achieve similar adherence levels. On a similar note, adherence among people with CF related diabetes (who typically have higher treatment burden since they need to incorporate insulin use in their treatment regimens [355, 361-363]) also did not differ from people without CF related diabetes.

While these findings within observational datasets indicate that treatment complexity does not offer sufficient explanation for low adherence, this is certainly not to say that increasing the number of prescribed nebulisers or a more complex treatment regimen would *cause* higher adherence.

4.4.6 Limitations

Prescribing decisions in the real world may be biased by clinicians prescribing more complex regimens only to those most able to cope.[212] Therefore, the lack of association between nature of treatment regimen and adherence should be interpreted with caution in this observational study. Likewise, it is also premature to conclude that treatment rationalisation would *cause* a decline in actual number of nebuliser doses taken (i.e. the “clinical effectiveness of adherence”), although treatment rationalisation is definitely not associated with an increase in the number nebuliser doses taken. This is because most of the ‘suboptimal prescriptions’ in this dataset are likely to be a response to low adherence, with treatment reductions agreed in an attempt to try increase the confidence or self-efficacy of people who were struggling to adhere with their previous treatment regimen. Previous studies in other long-term conditions have also shown that therapeutic inertia

was more likely among patients with low adherence (who were perceived by clinicians as less willing to accept efficacious treatments).[212] It may be that the number of nebuliser doses taken by adults with CF would also continue to decline if an effective treatment regimen was maintained instead of lowering the treatment targets. These important empirical questions are difficult to answer using observational datasets. Current methods of quantifying CF “adherence” without accounting for the effectiveness of a treatment regimen is another barrier to answering these important empirical questions.

The second limitation of this study is the relatively small sample size. An effect can only be detected in a small study if the effect size is sufficiently large.[232] For example, based on the confidence intervals reported in Table 4.4 (–20.7 to 1.3 for gender difference in adherence), this study is not adequately powered to detect difference in adherence of 10% between males and females. A 10% difference in adherence may well be clinically relevant and this study certainly does not exclude the possibility that females have lower adherence than males, especially since females were also less likely to be on I-neb[®] compared to males (for each calendar year, >60% of males were on I-neb[®] but <50% of females were on I-neb[®] – this is likely to reflect patient preference rather than indication bias because there is no clinical reason to target nebuliser type according to gender).

On the same note, the small number of people in the most affluent socioeconomic quintile (~15% of the sample) meant that the analysis was not powered to detect an adherence difference of 10% between people in the most affluent quintile and other deprivation quintiles. The lack of clear differences in adherence among the four other quintiles may also be the result of the way CF care is delivered in Sheffield, where frequent multidisciplinary team meetings develop explicit strategies to support people living in more deprived areas using interventions such as home visits, rather than a generalisable finding in other datasets. Throughout 2013 to 2016, the socioeconomic deprivation profile of adults on I-neb[®] is similar to adults not on I-neb[®], which suggests an equitable structure in terms of using appropriate devices to deliver preventative inhaled therapies in Sheffield. There is also a trend of improving adherence across all deprivation quintile, which suggests that no Sheffield adult is being left behind on the basis of socioeconomic deprivation.

Recognising the limitations of the Sheffield dataset, this thesis did not seek to separate out the potential influence of the two different forms of alternating treatment regimens – “on-off” regimen (which might represent the lowest “treatment burden” since a month on nebulised antibiotics is followed by a month off nebulised antibiotics which may allow self-regulatory resources to be replenished) vs continuous alternating regimen (which might represent the highest “treatment burden” since a person is continually on nebulised antibiotics and is required to alternate between different forms of antibiotics at a regular interval, which may require slightly different methods of administration, hence may undermine a stable context to maintain behaviour). Only eight out of 126 adults provided adherence data during on-off antibiotics treatment regimens, hence it would not be possible to reliably detect a difference.

Chapter 4, Section 5: Conclusions

Despite the limitations listed, this is the first systematic exploration of the relationship between a range of demographic & treatment factors and objective nebuliser adherence over a four year period. The Sheffield dataset is currently the largest EDC adherence dataset in CF with 18,303 weeks of adherence data from 126 adults with CF. Since all eligible adults receiving care at the Sheffield Adult CF centre are included in the dataset, this study has a lower risk of selection bias compared to other CF-related studies. Inclusion of all eligible adults also allows more appropriate interpretations of the findings from a whole system perspective. For example, the lack of clear differences in adherence between different socioeconomic deprivation quintiles noted in Sheffield could be interpreted in light of evidence suggesting an equitable structure to deliver preventative inhaled therapies in Sheffield whereas the UK CF registry data suggest that adults from more deprived areas were less likely to receive preventative inhaled therapies;^[150] i.e. there may be care delivery reasons for that particular finding in Sheffield, rather than assuming the finding is generalisable to other datasets.

Nonetheless, by confirming the important relationship between adherence and age found in previous studies using MPR data, it is clear that young adults with CF are particularly at risk of low adherence and perhaps targeted intervention is required for the 19–25 years age range. It is also important to account for age as a potential case-mix confounder when comparing adherence levels between different CF centres. Given the role of centre-comparisons and benchmarking in transforming the care of people with CF,^[346, 385-387] it is likely that comparisons using adherence as a quality indicator has the potential to drive improvement in medication adherence. However, centre-comparison is only meaningful and useful if confounding factors are appropriately adjusted for.

In addition, this study highlights the challenge of sustaining longer-term adherence and points towards the importance of exploring the potential role of habit to sustain long-term self-care – this is the objective of Chapters 5 & 6. There are also findings from this study which raise questions regarding the suitability of using the Leeds criteria to define *P. aeruginosa* status among adults with CF, and the adequacy of quantifying the implementation phase of adherence without taking into account the effectiveness of prescribed treatment regimens. Methods to define *P. aeruginosa* status and to quantify adherence are further explored as part of the PhD research, but are beyond the scope of this thesis.

Since a single-centre analysis such as this study may lack generalisability, further analyses using larger prospectively collected objective adherence datasets among other cohorts of adults with CF would be desirable. The on-going CFHH RCT (ISRCTN55504164) and CFHH improvement collaborative (ISRCTN14464661), which has recruited more than 500 and 200 participants respectively, will offer the opportunity to better understand how demographic and treatment factors can influence nebuliser adherence among adults with CF.

CHAPTER 5: AN EXPLORATORY MIXED METHODS STUDY COMPARING LOW AND HIGH NEBULISER ADHERERS

The literature review in Chapter 3 identified that most studies of adherence determinants among people with CF eschewed explicit psychological theory, focusing instead on the practical barriers and facilitators to adherence. Treatment burden, often operationalised as the duration, frequency and complexity of treatment regimens, is the focus of many studies seeking to explain low adherence in CF.

The Capability, Opportunity and Motivation (COM-B) model posits three factors necessary for any behaviour to occur: perception of capability, opportunity and motivation.[305] Hence, there is a need to understand adherence determinants from a broader perspective. Understanding nebuliser adherence also requires focusing not only on the barriers among people with low adherence, but those who consistently adhere. In Chapter 4, the Sheffield dataset found that some people can maintain consistently high adherence over many years. Similar findings have also been shown in other cohorts of people with CF.[176]

High-adherers may have better self-regulatory skills or resources (i.e. greater psychological capability), which may explain why the analyses in Chapter 4 found higher adherence to shorter-term *P. aeruginosa* eradication therapy compared to longer-term regimens. Previous studies have identified people with CF intentionally not using nebulisers [251, 252, 259] to cope with concurrent CF treatments while others have reported “on-off” inhaled antibiotics regimen to be more tolerable,[245] which may reflect a need to replenish self-regulatory capacity during non-use periods.[315]

High-adherers may perhaps be better able to routinise nebuliser use. ‘Routinisation’ (i.e. fostering of contextually stable and persistent behaviour patterns) has been reported as a facilitator of CF nebuliser use.[251, 259] This raises the possibility that long-term nebuliser adherence may be sustained by non-reflective motivational processes such as habit. Habit, i.e. a process by which situational cues (e.g. time) automatically generates an impulse towards enacting a behaviour (i.e. using nebuliser) [250] was discussed in Section 3.4. Habitual behaviours can be discerned into habitually instigated sequences (e.g. nebuliser use episodes that are triggered at the same time of day) and habitually executed actions (e.g. nebuliser use performed in an automated and unvarying sequence). While habitual instigation tendency is likely to predict the frequency of nebuliser use episodes,[328, 329] habitual execution tendency may perhaps also support adherence by making progression through the procedural intricacies of nebuliser use easier to perform.[328]

Habit forms through a process of ‘context-dependent repetition’, whereby repeated performance in the consistent presence of environmental cues (e.g. location or mood) reinforce the mental cue-action association.[250] Unstable contexts may thus preclude habit formation.[388] This may be one reason that ‘chaotic’ lifestyles, which lack structure and predictability, are associated with lower medication adherence.[389, 390]

Chapter 5, Section 1: Introduction

Previous studies of the determinants of nebuliser adherence among people with CF have been limited by a focus on self-reported adherence, reflective motivational constructs, and barriers among low adherers, rather than facilitators among high adherers. Theory suggests that both reflective and non-reflective processes influence medication adherence among adults with CF, but this has yet to be empirically explored.

The present study used objective adherence data to identify both low and high adherers, and investigated potential factors that may discriminate between these two groups with a focus on both reflective and non-reflective processes. Treatment burden (treatment complexity and perceived treatment burden), self-regulation, life chaos, habit ('non-specific', instigation, execution), intention, capability and opportunity were the hypothesised adherence predictors explored in this study. A mixed methods design [391] was used to quantify relationships between potential determinants and adherence, and also to offer in-depth insights into the specific beliefs, attitudes and values that may underpin such relationships.

Chapter 5, Section 2: Methods

5.2.1 Procedure

This was a mixed methods cross-sectional exploratory study among adults with CF, selected to represent high nebuliser adherence ($\geq 80\%$ annual adherence), and low nebuliser adherence ($< 50\%$ annual adherence). Adherence of $\geq 80\%$ is considered 'high' because such an adherence rate yields better health outcomes.[200, 392] Adherence of $< 50\%$ indicates a general tendency not to adhere, and is considered 'low'.

People with CF aged 16 or over were identified by their clinical team and sent a study information pack two weeks before their routine clinical visits. Data collection was timed to coincide with routine review visits at the CF centre. After review by their usual clinical team, which in accordance with standard procedures involved provision of personalised feedback on objective nebuliser adherence level, the PhD student (HZH) approached potential participants and invited them to take part. Those who consented were asked to verify the veracity of prescribed treatments as recorded in the medical notes. Next, they completed a questionnaire comprising measures of potential adherence predictors, and subsequently a face-to-face semi-structured interview. Interviews lasted 30-60 minutes to broadly explore participants' experiences around nebuliser use. The interview topic guide was sufficiently open to allow emergence of new insights (see Table 5.1). The topic guide was informed by the extant literature in similar clinical areas [259] and the clinical experience and expertise of the research team. It was refined after the first four interviews, taking into account the results of the initial four interviews.

Table 5.1: Topic guide for the semi-structured interview

The initial topic guide for the semi-structured qualitative interview:

Main questions	Additional questions	Clarifying questions
(A) Have you made any adaptations / changes to help you use your nebuliser?	<ul style="list-style-type: none"> • Clarify what adaptations / changes were made e.g. changes to routines, changes to lifestyle. • Clarify what makes it difficult for the participant to use his / her nebuliser ... • Clarify what strategies the participant use to overcome those difficulties ... • Clarify what makes it easier for the participant to use his / her nebuliser ... • Any suggestions / advice from the participant to help others use their nebuliser? 	<ul style="list-style-type: none"> • Can you please clarify what you meant by ...? • Can you please expand a little on ...? • Can you please give some examples of ...? • In particular, what do you think of ...?
(B) Have you used reminders / cues / routines to help you remember to use your nebuliser?	<ul style="list-style-type: none"> • Clarify what reminders / cues / routines that the participant has tried ... • Clarify what reminders / cues / routines work best for the participant ... • Any perceived advantages of a particular reminders / cues / routines? • Any perceived disadvantages of a particular reminders / cues / routines? 	

Additional questions for the iterated topic guide:

<ul style="list-style-type: none"> • Check whether in work / study. • What is the relationship between work / study with routine? • How does the use of nebuliser vary with the day of the week? Why? • How does the use of nebuliser vary with the time of day? Why? • What happens when “out of routine” – e.g. holidays • What is the support from family to manage nebuliser use (parents / partners / others)? • What is the support from the clinical team? What is the role of individual team members? Helpful / not? • If people describe symptoms – explore more. • If people describe effects of poor adherence / benefit of good adherence – explore more.

Digitally recorded interviews were transcribed verbatim. Participants were offered the option to review their own interview transcript for data verification.

All the participants were known to the PhD student who performed the interviews and analysed the data, since he worked as a doctor with the CF clinical team for ~18 months prior to data collection. However, nebuliser adherence is not typically an issue that entails detailed discussion between doctors and adults with CF in the centre, with physiotherapists taking a lead on this for the multidisciplinary team.

This study was approved by the London – Westminster Research Ethics Committee (REC reference: 15/LO/0328).

5.2.2 Participants

Participants were recruited from the Sheffield Adult CF Centre, which at the time of data collection (May to August 2015) had 203 registered patients aged ≥ 16 years diagnosed, to the UK CF Trust criteria,[348] as having CF. Eligible participants with CF used I-neb[®] as part of their routine treatment and had baseline objective annual adherence of either $\geq 80\%$ or $<50\%$. People in the palliative phase of disease, pregnant women, those with transplanted lungs or actively listed for lung transplantation, or lacking capacity to consent were excluded.

A target sample size of 20–24 participants (i.e. 10–12 people with $\geq 80\%$ adherence, 10–12 with $<50\%$ adherence) was set. This was deemed sufficient to achieve theoretical saturation in qualitative analysis,[393] while also feasible given a limited pool of eligible participants within a single CF centre. Of 36 eligible adults with CF (18 high, 18 low adherence) attending clinical reviews from May to August 2015, 20 participated (10 high, 10 low adherence; 56% recruitment rate) in this mixed methods study.

5.2.3 Measures

5.2.3.1 Demographic data and health outcomes

Demographic data were obtained from medical notes.

Best *lung function* was operationalised as the highest %FEV₁ calculated with the Knudson equation [394] for a 1-year period up to the day of recruitment.

Severity and frequency of *pulmonary exacerbations* were captured via total intravenous (IV) antibiotic days over the same 1-year period.

5.2.3.2 Nebuliser adherence

Objective nebuliser data were downloaded from I-neb[®]. The implementation phase of adherence was calculated as a percentage between total amount of medications used against the dose agreed between clinicians and adults with CF.

5.2.3.3 Hypothesised predictors of adherence

Unless stated, all hypothesised predictors were self-reported using items with which participants rated agreement from 1 (strongly disagree) to 7 (strongly agree). These items are listed in Table 5.2.

Table 5.2: The 28 items used in the questionnaire

1.	Pleasure and fun sometimes keep me from getting work done – <i>to measure self-regulation</i>
2.	I do not like to make appointments too far in advance because I do not know what might come up – <i>to measure life chaos</i>
3.	My life is unstable – <i>to measure life chaos</i>
4.	I do certain things that are bad for me, if they are fun – <i>to measure self-regulation</i>
5.	Keeping a schedule is difficult for me – <i>to measure life chaos</i>
6.	I often act without thinking through all the alternatives – <i>to measure self-regulation</i>
7.	I am good at resisting temptation – <i>to measure self-regulation</i>
8.	My life is organised – <i>to measure life chaos</i>
9.	I wish I had more self-discipline – <i>to measure self-regulation</i>
10.	I have a hard time breaking bad habits – <i>to measure self-regulation</i>
11.	My routine is the same from week to week – <i>to measure life chaos</i>
12.	My daily activities from week to week are unpredictable – <i>to measure life chaos</i>
13.	People would say that I have iron self- discipline – <i>to measure self-regulation</i>
14.	Sometimes I can't stop myself from doing something, even if I know it is wrong – <i>to measure self-regulation</i>
15.	Using my nebuliser is something I do without thinking – <i>to measure non-specific habit</i>
16.	My nebuliser treatment is too time-consuming to manage within my daily life – <i>to measure 'subjective' treatment burden</i>
17.	Using my nebuliser is something I do without having to consciously remember – <i>to measure non-specific habit</i>
18.	If I wanted to, nothing gets in the way of me using my nebuliser – <i>to measure opportunity</i>
19.	If my nebuliser is working properly, I would feel capable of using my nebuliser – <i>to measure capability</i>
20.	I intend to use my nebuliser – <i>to measure intention</i>
21.	Using my nebuliser is something I do automatically – <i>to measure non-specific habit</i>
22.	I feel I have adequate opportunity to use my nebuliser – <i>to measure opportunity</i>
23.	Using my nebuliser is something I start doing before I realise I'm doing it – <i>to measure non-specific habit</i>
24.	I want to use my nebuliser – <i>to measure intention</i>
25.	My nebuliser treatment makes my daily life more difficult – <i>to measure 'subjective' treatment burden</i>
26.	I could overcome barriers to using my nebuliser if I invest the necessary effort – <i>to measure capability (self-efficacy)</i>
27.	Deciding to use my nebuliser is something I do without having to consciously remember – <i>to measure instigation habit</i>
28.	Once I have decided to use my nebuliser, using my nebuliser is something I do without having to consciously remember – <i>to measure execution habit</i>

Treatment burden was measured in two ways. 'Objective' burden was measured via the Treatment Complexity Score,[213] which assigns a value of 1, 2 or 3 (3 = highest burden) to the 37 CF maintenance therapies, producing a single score from 0 (no burden) to 72 (highest burden). 'Subjective' burden was self-reported using two items modified from the CF Questionnaire-Revised,[395] e.g. "My nebuliser treatment makes my daily life more difficult"; $\alpha = 0.74$.

Self-regulation was measured with eight items from the Brief Self-Control Scale,[396] e.g. “I am good at resisting temptation”; $\alpha = 0.68$.

Life chaos was measured via six items from the Modified Confusion, Hubbub and Order Scale Life,[389] e.g. “My life is organised”; $\alpha = 0.68$.

Habit strength was measured in three ways. The habitual nature of nebuliser use was measured using items from the Self-Report Behavioural Automaticity Index (SRBAI).[336] A sequence of ‘habitual’ behaviour can be habitually triggered (habitual instigation) and/or automatically performed to completion after being triggered (habitual execution).[328] As originally formulated however, the SRBAI does not distinguish between habitual instigation or execution, but rather offers a non-specific habit measure that potentially incorporates elements of instigation and execution.[328] The original SRBAI wording formulation was used to measure *non-specific habit* with four items (e.g. “Using my nebuliser is something I do without thinking”; $\alpha = 0.82$). To aid identification of the precise location of habit in nebuliser use sequences, *habitual instigation* and *habitual execution* were also measured. To minimise participant burden, habitual instigation and execution were each measured using a single item from the SRBAI, which differed only in the item stem (instigation: “Deciding to use my nebuliser ...”; execution: “Once I have decided to use my nebuliser, using my nebuliser ...” [“... is something I do without having to consciously remember”]).[328] This item was selected on the basis that, of four SRBAI items, it showed the strongest item-total agreement in pilot data among 15 adults with CF.[397]

Intention (e.g. “I intend to use my nebuliser”; $\alpha = 0.88$), *opportunity* ($\alpha = 0.38$) and *capability* ($\alpha = -0.43$) were each measured using two items adapted from the COM-B Self-Evaluation Questionnaire.[398] Lack of reliability suggested that items were measuring different facets of opportunity and capability (e.g. control over external barriers vs self-efficacy [399]). Opportunity and capability were thus represented in the analysis by two single items, labelled according to which specific facet was assessed (opportunity: “If I wanted to, nothing gets in the way of me using my nebuliser” [hereafter, ‘opportunity, absence of obstacles’], “I feel I have adequate opportunity to use my nebuliser” [‘opportunity, generic’]; capability: “If my nebuliser is working properly, I would feel capable of using my nebuliser” [‘capability, external control’], “I could overcome barriers to using my nebuliser if I invest the necessary effort” [‘capability, self-efficacy’]).

5.2.4 Analysis

5.2.4.1. Integration between quantitative and qualitative components

Quantitative and qualitative data were collected concurrently.[391] The “following a thread” technique was used to integrate analyses.[400] Key differences (‘threads’) observed in initial quantitative analysis between high and low adherers prompted consultation of qualitative data to aid interpretation and key insights (‘threads’) obtained from initial qualitative analysis prompted consultation of quantitative data.

5.2.4.2 Quantitative data analysis

Quantitative analysis involved describing and comparing characteristics of 'high' and 'low adherers'. Due to the pragmatic but small sample size, null-hypothesis significance testing was not performed. Thus, effect sizes and confidence intervals are reported, but not p values.[401] Due to a non-normal data distribution and presence of outliers, non-parametric methods [402] were used to estimate group differences and confidence intervals for all continuous variables. This method assumes the two groups have the same distribution shifted by a fixed parameter. The shift parameter is not necessarily the difference in medians, rather it is the median of all possible differences. For categorical data, difference in proportions and confidence intervals were calculated using the Wilson procedure without continuity correction.[403] Linear correlation between continuous variables was determined using non-parametric method (Spearman's rho).[404]

Due to the strong association between age and adherence found in the analyses of Chapter 4, adherence levels were mapped across the four age categories used in previous studies [200, 283] and in Chapter 4: ≤ 18 years ($N = 5$), 19–25 years ($N = 5$), 26–34 years ($N = 6$), ≥ 35 years ($N = 4$). For variables shown to differentiate high and low adherers, follow-up analyses documented scores of these variables across the four age categories. All pertinent effects observed for non-specific habit were also followed up with analyses to determine whether such effects were attributable to habitual instigation or habitual execution.

In light of a 'thread' that emerged from qualitative analysis, further exploratory analyses of habit were run. In these analyses, the sample was dichotomised into those who 'had habit' (high level of automaticity, habit score ≥ 4 , i.e. at or above the scale midpoint [405]) or 'had no habit' (habit score < 4), on each of the three habit measures (i.e. had non-specific habit vs no non-specific habit, had instigation habit vs no instigation habit, had execution habit vs no execution habit).

All quantitative analyses were run using R v3.3.0 (www.r-project.org). Graphs were generated using Prism v7 (GraphPad Software).

5.2.4.3 Qualitative data analysis

Qualitative data were thematically analysed using a general inductive approach [406] involving data familiarisation, generating initial codes, and iteratively searching for, reviewing, defining and naming themes. NVivo v10 (QSR International) was used to organise analysis. Data were collected and analysed concurrently by the interviewer (the PhD student), with two experienced qualitative researchers verifying the appropriateness of data interpretations (JB, BG).

The PhD student read all transcripts several times for familiarisation and generated initial codes. JB independently analysed six (30%) transcripts to search for themes and verified that theoretical saturation had been reached at 17 interviews, as no further insights emerged from subsequent analyses. A shared analytic framework was agreed upon through discussions between the two coders. The PhD student then extracted pertinent data using the agreed coding framework. At this stage, it was apparent that some of the emergent themes tied up closely with the concept

addressed in the questionnaire, and this helped the organisation of codes into broader themes. Finally, these themes were reviewed and refined in discussion with BG.

Chapter 5, Section 3: Results

5.3.1 Quantitative results

Low adherers tended to be younger and had higher %FEV₁, yet had more severe or frequent pulmonary exacerbations, i.e. greater IV antibiotics use; median of differences 10 days (95% CI –4 to 31 days); see Table 5.3.

Table 5.3: Clinical characteristics and outcomes of high (*N* = 10) and low (*N* = 10) adherers

	Low adherers (<i>N</i> = 10) Median (IQR)	High adherers (<i>N</i> = 10) Median (IQR)	Median of differences between groups (95% CI)
% Nebuliser adherence in previous year	28.0 (5.3 to 46.0)	94.9 (86.7 to 108.5)	–69.1 (–92.6 to –48.9)
Age in years	21.5 (19.3 to 31.3)	30.0 (18.0 to 42.0)	–5.3 (–13.0 to 3.0)
Female ‡	3 (0.30)	5 (0.50)	0.20 (–0.20 to 0.53)
Best %FEV ₁ for the previous year	88.0 (80.0 to 96.3)	77.0 (56.0 to 86.0)	13.0 (–4.0 to 31.0)
Total IV days for the previous year	13 (0 to 50)	7 (0 to 16)	10 (–4 to 31)

‡ For gender, the proportion of female participants in each group and difference in proportion (95% CI) were displayed

In keeping with the findings in Chapter 4, median adherence was lowest among participants aged 19–25 years (25.3%, IQR 3.3% to 93.8%), and highest among those aged ≥35 years (94.9%, IQR 58.4% to 96.2%). Participants of this study have similar clinical characteristics in comparison to other non-participating adults in the CF centre (see Table 5.4), suggesting that the samples within each adherence group are representative of the wider Sheffield population.

Table 5.4: Clinical characteristics of the participants in comparison to the local population of adults with CF that did not participate, stratified according to adherence levels

	Low adherers, participants (<i>N</i> = 10) median (IQR)	Low adherers, non-participants † (<i>N</i> = 42) median (IQR)	High adherers, participants (<i>N</i> = 10) median (IQR)	High adherers, non-participants † (<i>N</i> = 18) median (IQR)
% Nebuliser adherence in previous year	28.0 (5.3 to 46.0)	23.1 (10.7 to 34.6)	94.9 (86.7 to 108.5)	96.7 (89.8 to 99.3)
Age in years	21.5 (19.3 to 31.3)	25.0 (20.0 to 32.0)	30.0 (18.0 to 42.0)	26.0 (17.8 to 28.0)
Female ‡	3 (0.30)	20 (0.48)	5 (0.50)	4 (0.22)
Best %FEV ₁ for the previous year	88.0 (80.0 to 96.3)	80.5 (61.0 to 96.0)	77.0 (56.0 to 86.0)	85.0 (73.3 to 89.5)
Total IV days for the previous year	13 (0 to 50)	22 (9 to 35)	7 (0 to 16)	2 (0 to 22)

† For non-participants, data from 01 January 2015 to 31 December 2015 were used.

‡ For gender, the proportion of female participants in each group and difference in proportion (95% CI) were displayed

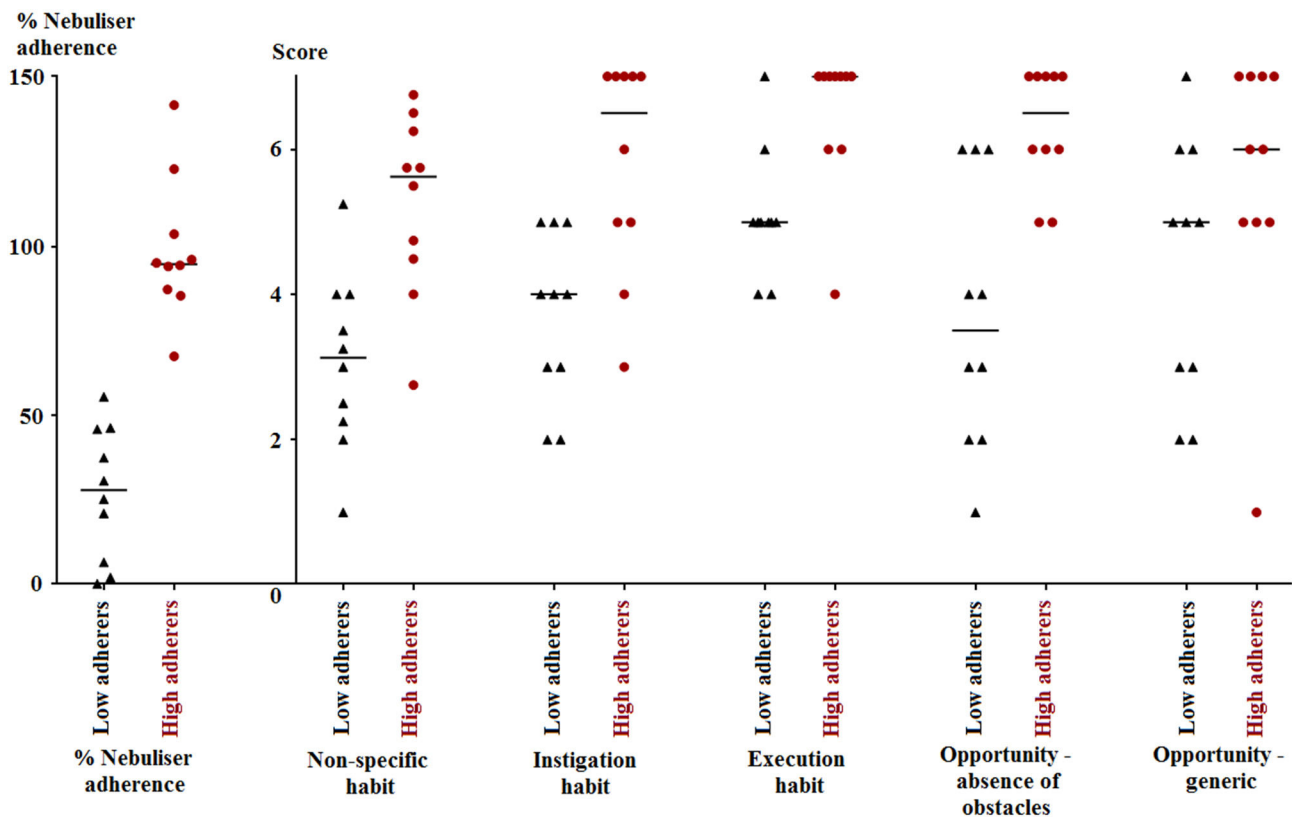
Scores on most potential predictors were similar across both groups (see Table 5.5 and Figure 5.1). However, low adherers had slightly lower self-regulation scores (median of differences -0.8 , 95% CI -1.4 to 0.0). There were moderate to large differences in opportunity and non-specific habit scores between the two groups of participants, and a strong positive correlation between those two variables ('Opportunity, absence of obstacles' $r = 0.66$, 95% CI 0.30 to 0.85 ; 'Opportunity, generic' $r = 0.75$, 95% CI 0.46 to 0.90). Follow-up analyses suggested that opportunity-habit correlations were for instigation habit ('Opportunity, absence of obstacles' $r = 0.47$, 95% CI 0.03 to 0.75 ; 'Opportunity, generic' $r = 0.51$, 95% CI 0.09 to 0.78), rather than execution habit ('Opportunity, absence of obstacles' $r = 0.43$, 95% CI -0.01 to 0.73 ; 'Opportunity, generic' $r = 0.34$, 95% CI -0.11 to 0.68).

Table 5.5: Psychological factors among high ($N = 10$) and low ($N = 10$) adherers

	Low adherers ($N = 10$) Median (IQR)	High adherers ($N = 10$) Median (IQR)	Median of differences between groups (95% CI)
Treatment complexity score	14.5 (10.0 to 15.3)	15.5 (10.0 to 16.5)	-1.0 (-5.0 to 4.0)
Perceived treatment burden	2.3 (1.4 to 3.6)	1.8 (1.0 to 3.5)	0.5 (-1.0 to 2.0)
Self-regulation	4.6 (3.7 to 4.9)	5.4 (4.5 to 5.8)	-0.8 [-1.4 , 0.0]
Life chaos	4.5 (3.8 to 5.3)	5.4 (4.7 to 5.7)	-0.8 [-1.7 , 0.2]
Intention	6.8 (6.4 to 7.0)	7.0 (6.3 to 7.0)	0.0 [-0.5 , 0.5]
Capability, external control	6.0 (4.0 to 7.0)	7.0 (7.0 to 7.0)	-1.0 (-3.0 to 0.0)
Capability, self-efficacy	6.0 (4.8 to 6.0)	6.5 (2.5 to 7.0)	-1.0 (-1.0 to 3.0)
Opportunity, absence of obstacles	3.5 (2.0 to 6.0)	6.5 (5.8 to 7.0)	-3.0 (-4.0 to -1.0)
Opportunity, generic	5.0 (2.8 to 6.0)	6.0 (5.0 to 7.0)	-1.0 (-3.0 to 0.0)
Habit:			
Non-specific habit	3.1 (2.2 to 4.0)	5.6 (4.4 to 6.3)	-2.3 (-3.5 to -1.0)
'Instigation habit'	4.0 (2.8 to 5.0)	6.5 (4.8 to 7.0)	-2.0 (-3.0 to -1.0)
'Execution habit'	5.0 (4.8 to 5.3)	7.0 (6.6 to 7.0)	-2.0 (-2.0 to -1.0)

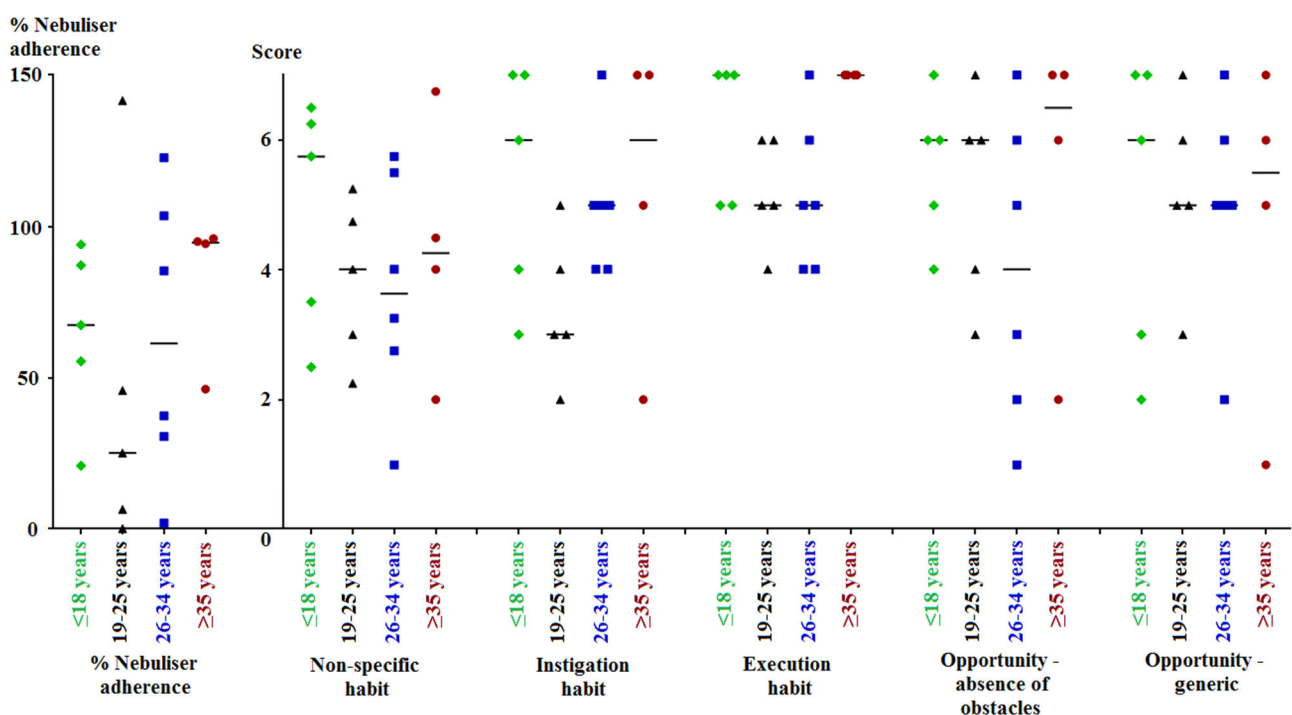
Low adherers reported non-specific habit scores that were on average 2.3 points lower than high adherers on a 1 to 7 scale (95% CI -3.5 to -1.0). 'Instigation habit' may have better differentiated between high adherers (median 6.5, IQR 4.8 to 7.0) and low adherers (median 4.0, IQR 2.8 to 5.0); median of differences 2.0 (95% CI 1.0 to 3.0), than did 'execution habit' (high adherers median 7.0, IQR 6.6 to 7.0; low adherers median 5.0, IQR 4.8 to 5.3; median of differences 2.0, 95% CI 1.0 to 2.0). High adherers were more likely to 'have non-specific habit' (9/10 high adherers vs 3/10 low adherers; difference in proportion 0.60, 95% CI 0.17 to 0.81). High adherers (9/10) tended to be more likely to 'have instigation habit' than did low adherers (6/10; difference in proportion 0.30 95% CI -0.08 to 0.60)). All participants were classified as 'having execution habit'.

Figure 5.1: Scatter-dot plots displaying the differences in nebuliser adherence, habit and opportunity scores for low vs high adherers



Follow-up analyses of habit and opportunity scores according to age showed that participants aged 19–25 years (lowest adherence) reported the lowest instigation habit scores (median 3.0, IQR 2.5 to 4.5), whilst adults aged ≥35 years (highest adherence) reported correspondingly high instigation habit scores (median 6.0, IQR 2.8 to 7.0). In contrast, opportunity scores were relatively similar for the different age groups (see Figure 5.2).

Figure 5.2: Scatter-dot plots displaying the differences in nebuliser adherence, habit and opportunity scores according to the four age groups



5.3.2 Qualitative results

Four themes underpinned participants' experience of using inhaled therapy: 'awareness & experiences of health consequences', 'cues, routinisation & automaticity', 'prioritisation' and 'coping with treatment burden'.

5.3.2.1 Awareness and experiences of health consequences

Knowledge and experience of the health benefits of using, and not using nebulised treatments appeared important in motivating nebuliser use for both low and high adherers, regardless of age.

[Not using] my DNase will [make it] harder to cough up and get rid of bugs, get rid of all the mucus. [Not using] my Promixin means my Pseudomonas will probably come back again and I don't want to get down that route again.

P17, high adherence, ≤18 years

Symptoms during acute periods of ill health (for example during pulmonary exacerbations) reportedly made nebuliser use seem more effortful. However, high adherers took steps to persist with their treatments in spite of such difficulties ('If I've got to take it, doesn't matter if I'm unwell or well, I've still got to take it in that day'; P3, high adherence, ≥35 years), and indeed for some, ill-health increased motivation to use nebuliser treatment, as a means to avoid further worsening of health.

Two low adherers (one 19–25 years, another 26–34 years) relied exclusively on experiencing symptoms to prompt their nebuliser treatment, such that they did not use nebulisers when they felt well.

I can have good days where I feel good for a week, where doing any treatment doesn't come into mind. [But on other days] I might wake up and feel shocking. That'll prompt me [to use my nebuliser], and then it'll take me a bit to recover.

P15, low adherence, 26–34 years

Most nebulised treatments have no immediate noticeable impact, and both the two low adherers reported that the relative 'invisibility' of health benefits made it difficult for them to appreciate the necessity of using nebuliser.

If somebody sees me at gym, I just want to do gym. I want to get in shape more. You can see a physical shape in yourself. You can't see your lung, can you? You can't see what's going off there. It's not like you can look [inside] them.

P7, low adherence, 19–25 years

Some participants preferred treatments with more immediate and tangible benefits (i.e. hypertonic saline, which typically stimulates vigorous coughing and increases sputum expectoration) over a treatment with less visible consequence (dornase alfa or DNase, which more effectively improves lung function but generally produces no immediate perceivable changes [407, 408]).

Hypertonic saline makes an instant difference. Whereas DNase I don't know if it does [make a difference] or not, but I just believe in it. [...] Hypertonic saline definitely has a massive positive effect on my chest. So for that reason, I don't miss [opportunities to use my hypertonic saline] ... but [this is] not [necessarily the case for] my DNase

P13, high adherence, ≥35 years

High adherers often reported experiencing benefits of nebulised treatments, or had experienced consequences of previous low adherence.

When I first started [using my nebuliser] I remember the benefit with your lung function ... it also means that you don't have to go in [to hospital] for [intravenous antibiotics] as often.

P9, high adherence, 26–34 years

I don't get half as chesty using [my nebuliser regularly] now, than when I didn't use it.

P1, high adherence, ≥35 years

While high adherers reported having in the past been prompted by experiencing symptoms, for most, nebuliser motivation appeared to have shifted towards being regulated by anticipation of ill-health arising from non-use. For example, two high-adherers (one 19–25 years, another 26–34 years) reported having experienced highly aversive severe pulmonary exacerbation in the past due to non-adherence, and this served as a motivational reminder of the importance of nebuliser use. However, experiencing symptoms or recalling symptomatic episodes did not appear to be the predominant trigger for high adherers; rather, for most high adherers, nebuliser use had become embedded within their everyday routines and was no longer directed by deliberative reasoning processes:

If I've missed my morning [nebulised treatment], by about 3 o'clock I can feel in me that I need to have [my nebulised treatment].

P13, high adherence, ≥35 years

5.3.2.2 Cues, routinisation and automaticity

Establishing a 'treatment routine' appeared important and the term "routine" was spontaneously mentioned by most participants. Nebuliser use was commonly incorporated into existing CF-related treatment routines or as a standalone medication activity routine within ostensibly unrelated daily activities.

If I'm taking my Promixin, I'll take it with my other medication at night, because I have other medication at night as well.

P1, high adherence, ≥35 years

First thing in a morning, I take my dogs out, come back, then the first thing I do is go to the fridge, get my DNase out. It's just a habit, every day.

P3, high adherence, ≥35 years

All high adherers described automatically 'remembering' to use their nebuliser. High adherers seemed to have more durable routines and described finding their treatments less burdensome due to routinisation.

Once I have fixed a routine that works for me ..., I can [use my treatments] all the time. I suppose I don't have to think about it. [...] I am not constantly having to make adjustments.

P12, high adherence, 26–34 years

Although low adherers also described automaticity to a certain extent, they tended to describe a more 'reflective' process of remembering to use their nebulisers.

[Nebulised medication] is probably the only drug I have to think about doing it, I have to gear myself up to using it. With my oral medications, basically I just incorporate that into my lifestyle ... but with my nebulisers, I have to sort of prepare myself to have them.

P16, low adherence, ≥35 years

Some low adherers struggled to incorporate nebuliser use into their existing routines due to irregular lifestyle, sometimes due to busy and unpredictable working patterns.

I'd have to finish work, because that's work. Then I'd come home tired and exhausted ... and that's why I normally [missed my evening nebuliser], because I'm asleep. [...] When I'm on the routine of taking the nebuliser, [I always bring it] to work but I don't always get the opportunity to use it during work because it's busy up to [the point of] me going home.

P15, low adherence, 26–34 years

In the absence of routine, low adherers were more dependent on external reminders, such as reminders from family and friends, or typically short-lived motivational boosts arising from discussions with health professionals.

My partner reminds me [to take my nebulisers]. [I also get reminders] from clinic visits, with getting prompts to take my nebuliser. [The effects from those reminders] will last for a week or so.

P15, low adherence, 26–34 years

Historical experience of consistent nebuliser use, such as in childhood, may have contributed to the development of a good 'nebuliser routine' among high adherers. Childhood experience appeared more relevant for adolescents and younger adults, compared to older adults.

I do my DNase in the afternoon [...]. It is just how I have always done it, because when I was younger I always did my Promixin before school and then as soon as I got home from school about four o'clock, I used to do my DNase.

P20, high adherence, ≤18 years

Both low and high adherers also described using self-regulatory techniques, such as using objective feedback from the nebuliser to monitor their adherence, or environmental restructuring to support their nebuliser routines ('I always put my I-neb near where I sit for my breakfast in the morning as a prompt'; P10, low adherence, 26–34 years). Similarly, both low and high adherers reported that weekends, evenings out, holidays, or other 'unexpected' events had the potential to disrupt typical behaviour patterns.

When I go out with my mates, I still try to have my morning Promixin and DNase. I'll have all my [oral medications first] and go about with my business. Comes to seven, eight o'clock I think alright, I'll start getting ready. But, suppose one of my mates is picking me up at half past seven and its quarter to seven, I think you know, I've got to get ready [so I can't use my nebulisers now].

P18, low adherence, 19–25 years

I do miss some [of my nebulisers], I am not perfect but that's normally because I am going to be late for work, or I have done something at night which I have not expected to do and I am really tired when I get in. They are they times when I normally miss it, but it is very rare.

P17, high adherence, ≤18 years

Such disruptions removed contextual triggers to nebuliser use, and by so doing also increased the amount of conscious effort required to use the nebuliser, both of which increased the likelihood of forgetting to use nebulisers:

It is just your time, your working days and other commitments. When you have other things, you sit down thinking of other things and the time goes on and you become tired. Then the time starts ticking away and it becomes a bit of a chore if you are tired.

P16, low adherence, ≥35 years

The only time it gets hard is if I have been out all day, or have been out late at night. Then if I have got my DNase to do, I have to wait another 45 minutes before I can do my Promixin or TOBI, but I still never really find it difficult to fit it in.

P20, high adherence, ≤18 years

However, high adherers seemed to be better able to create routines that were less amenable to potential disruption, or to shield their routines against experienced disruptions. They reported anticipating disruptions and overcoming these disruptions by planning of preparatory behaviours within newfound circumstances.

Even on the drive home, I will make sure I'll have the flutter valve in the car, so I get home and just to have the nebuliser, so I don't have to get home then have the flutter valve and then have the nebuliser.

P11, high adherence, 26–34 years

One low-adherer acknowledged the need to mitigate the impact of contextual changes, but did not view adaptation as necessary to short-term contextual changes:

If I was going on holiday for a week or two weeks, I would then obviously take my equipment and medication with me. If just for a few days you might think "I'll be all right, I'll not [bring my equipment]", then it's the matter of getting back into that routine.

P14, low adherence, 26–34 years

Perhaps as a consequence of better planning, high adherers reported that their lifestyle was more 'supportive' of nebuliser use.

5.3.2.3 Prioritisation

High adherers reportedly prioritised their nebulised treatments over other activities, sometimes even over other equally important tasks ('Say for example I overslept, I would do my [nebuliser] treatment but I'll skip breakfast'; P9, high adherence, 26–34 years). A high adherer reported prioritising her treatment routine when taking a new job:

When I started the new job, [the employers] did say when is best for you to do the hours and I suppose I kind of answered that knowing that it would be better for me to be around in the afternoons and I do actually quite like the routine that I have got going now, so I do sort of try and fit around other people but ultimately, I wouldn't commit to a routine that I know that I couldn't manage whilst also doing all my treatments. [...] My work routine has some advantages because my treatment can always come first.

P12, high adherence, 26–34 years

Placing a low priority on nebuliser use was problematic for two reasons. Firstly, pursuit, and at least temporary prioritisation, of other tasks could lead them to forget using their nebulised treatments. For some, forgetting on one occasion could lead to a longer-term derailment of adherence:

When I'm having [my nebulised treatment] and I'm constantly having them, then it's constantly on your mind all the time. But if maybe I had a couple of days off nebulisers, because I forgot it or run out, or left my nebuliser at home ... then it just snowballs from there, and you just forget.

P15, low adherence, 26–34 years

Secondly, the completion of prioritised tasks could mentally exhaust adults with CF, so that by the time all higher-priority tasks were completed they lacked the motivation or self-regulatory capacity to use nebulised treatments.

We have exams at the minute and, as much as [using nebuliser] should have been important, I think it just seemed less important because I've had a lot of exams and University, stuff like that.

P6, low adherence, 19–25 years

Low mood or depression, and stressful life circumstances such as preparing for university examinations reportedly led to temporary shifts in goal prioritisation, or depleted self-regulatory capacity to use nebulised treatment, so potentially leading to participants 'losing [their] routine' (P4, low adherence, ≤18 years):

I think it's just when I'm tired ... I'm stressing out over Uni and stuff like that, I just kind of blanked out what I'm not doing at that minute.

P6, low adherence, 19–25 years

A participant with high adherence also mentioned attending to stressful other tasks as a potential barrier to nebuliser use, but reported having a strategy for coping with the effects of stress.

Doing the other [tasks unrelated to nebuliser use] makes me more stressed, so I try and take a step back and calm down, do a bit less.

P12, high adherence, 26–34 years

5.3.2.4 Coping with treatment burden

Using nebulised treatment involves multiple steps, which can be time-consuming. Treatment was seen as burdensome by both high and low adherers, who reported burden related to the number of nebulised medications required, the sequence and timing of nebulised medications, and time and effort required to prepare and use nebuliser machine and along with other concurrent CF treatments.

Cleaning [the nebuliser] is definitely something that gets side-lined ... I just don't do that enough. And I think it's because it's about priorities and I definitely prioritise actually doing the nebuliser over the maintenance side of it.

P12, high adherence, 26–34 years

Perceived treatment burden was heightened when participants were tired, stressed or otherwise mentally depleted. However, those with high adherence appeared to cope better with the burden.

[The amount of treatment] wouldn't influence how I take [my treatment]. I think I would try to take it even if [there are lots of treatments]. If I need to take, I would.

P8, high adherence, 19–25 years

Those with significant amounts of other CF treatments also reported struggling to understand and resolve potentially inconsistent information from health professionals about using their nebuliser, and balancing nebuliser with other forms of CF treatments.

There is a bit of, sort of, argument [among the healthcare professionals] about whether I should or should not start this treatment that I would normally have on a regular basis. I think things like that can interfere with my [adherence]. It's like [someone asking me to check my] diabetes control every day and having to do my I-neb® every day. It's just difficult [to be doing everything].

P10, low adherence, 26–34 years

Due to perceived burden, both high and low adherers also described various other 'short-cuts' to help them make their treatments more manageable. Examples include using technology or pre-mixing nebulised medications to reduce treatment time, compensating for missed doses by using extra medications when able, taking 'treatment holidays' to replenish self-regulatory capacity and using distractions to deal with boredom experienced when inhaling nebulised medication.

With my promixin '...' sometimes what I find myself doing is when I've run out, I'll mix 30 vials up or so. [...] Mixing them all up and doing them so I know they're all here ready to go, makes me think: "right, I'll have them, I'll take them."

P18, low adherence, 19–25 years

Several high adherers described effective time management and planning as key adaptations to minimise treatment burden and so enable nebuliser use. Time management strategies took the form of altering leisure or work routines, and creating an optimal time window of nebuliser use to both facilitate remembering and allow adequate time to complete use.

For example, if I know the latest I can be in at work is nine o'clock, I'll make sure to get up in time to allow me plenty of time to get up, have a shower, do my physio, nebuliser, have breakfast, so I'm not missing that, and basically then get ready as I normally would.

P9, high adherence, 26–34 years

I had a paper round, so it was as soon as I got in from my paper round, I used to do my DNase and my Promixin in the morning, so I did my DNase, did my paper round and do my Promixin when I got back. But now I have changed it round so I do Promixin and DNase at night because I have got more time at night and I do my Promixin first thing in the morning.

P17, high adherence, ≤18 years

Social support from family and friends offered another way of reducing treatment burden, with some participants receiving direct practical help with the processes involved in using the nebuliser, for example with cleaning the nebuliser, or indirect help to free up time to use their nebulised treatments.

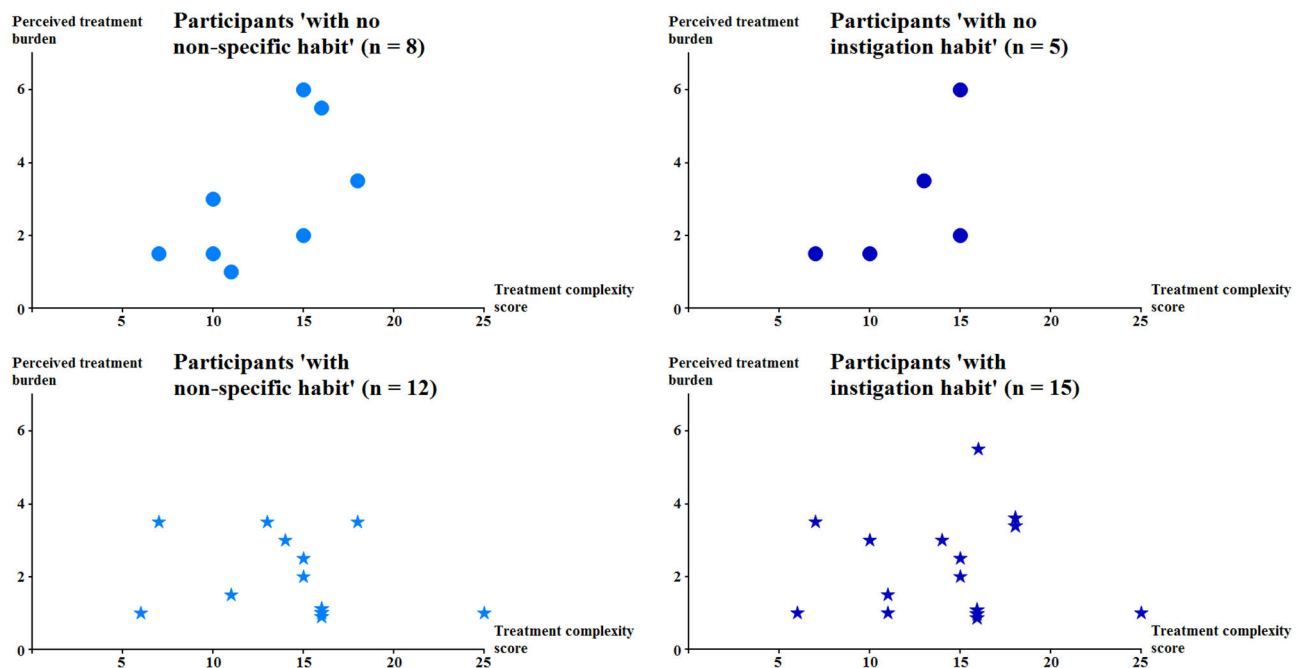
For instance my mum comes and cleans for me every Friday so that means that I can spend time doing my treatment, doing all the other things that I need to do and not getting frustrated by sitting doing my treatment in a dirty chaotic house. Nobody can do my nebulisers for me or do me Acapella for me, but there is lots of other stuff that can be done to help me dedicate my time to that, and that is essential.

P12, high adherence, 26–34 years

5.3.3 Follow-up quantitative analysis

In light of qualitative findings that routinisation reduced perceived treatment burden, follow-up quantitative analyses were run to explore whether relationships between treatment complexity and perceived burden differed according to the presence or absence of non-specific habit and instigation habit. No such analysis was run for execution habit, since every participant 'had execution habit'. Participants 'with no non-specific habit' ($N = 8$) showed a moderately strong linear correlation between objective treatment complexity and perceived treatment burden ($r = 0.64$, 95% CI -0.12 to 0.93), see Figure 5.3. Those 'with non-specific habit' ($N = 12$) showed no such relationship ($r = -0.29$, 95% CI -0.74 to 0.34).

Figure 5.3: Scatter plots displaying the relationships between perceived treatment burden and objective treatment complexity according to the absence or presence of habit



Similar results were obtained according to instigation habit, with a strong linear correlation between treatment complexity and perceived burden ($r = 0.79$, 95% CI -0.31 to 0.99) among those 'with no instigation habit' ($N = 5$), but no relationship between the two variables ($r = 0.04$, 95% CI -0.48 to 0.54) among those 'with instigation habit' ($N = 15$).

The consistency of findings across the two habit measures suggests that effects of non-specific habit on burden may be more precisely attributed to habitual instigation.

Chapter 5, Section 4: Discussion

Adults with low (<50%) annual nebuliser adherence patterns were typically younger and had better lung function (and so generally healthier), yet still required more intravenous antibiotics than did 'high adherers' ($\geq 80\%$). High adherers reported stronger habit and described habit helping to alleviate treatment burden. Habitual instigation – i.e. automatically 'remembering' to use nebulisers – appeared to differentiate between high and low adherers, and reduced the impact of treatment complexity on perceived burden, such that even complex treatment was not seen as burdensome. High adherers reported having and seizing more opportunities to use nebuliser, and perceived opportunities correlated positively with habit. Due to small sample size, findings should be considered preliminary, and require replication in adequately powered studies. Nonetheless, they offer tentative evidence that adherence interventions in adults with CF might be more effective by targeting development of routines to instigate nebuliser use, and identifying opportune moments for nebuliser use.

Echoing previous studies among people with CF,[5, 197, 199, 200] this study found that young adults aged 19–25 years had lowest adherence. Age-related differences in adherence may reflect the social, cognitive and contextual turbulence that characterises adolescence and early adulthood.[409] Partaking in ‘risky behaviours’ has been hypothesised to be part of identity explorations among younger adults, as one may desire to experience a wide range of experience before settling into the responsibilities of adult life.[410] Adolescents also spend more time with peers and those with CF might prioritise socialising and ‘appearing normal’ (i.e. not making CF visible) over nebuliser use.[252] Major life events such as moving home or starting employment are common [409] and may deplete self-regulation resources,[411] making it more difficult for younger adults to consistently use their nebuliser. Interestingly, in interviews, all participants regardless of age showed awareness of nebuliser use importance and reported strong intentions. This is also corroborated by the quantitative analysis of intention scores. Age differences in adherence therefore do not appear attributable to differences in treatment beliefs or intention strength.

There was, however, potential evidence of different motives for nebuliser use between high adherers and low adherers. First, high adherers with lower lung function (who tended to be older) reported they were often symptomatic when they missed their nebuliser, whereas low adherers with higher lung function (who tended to be younger) were unlikely to notice any short-term difference when not using their nebuliser. Salient negative health outcomes thus appear to trigger nebuliser use. Second, some of the low adherers depended almost exclusively on the actual experience of ill-health to prompt nebuliser use, such that nebuliser was used only when pulmonary exacerbation has occurred. By contrast, high adherence was more typically motivated by the anticipation of ill-health arising from non-use, such that nebulisers were actually used to prevent exacerbation. This echoes a literature demonstrating that anticipating regret for choosing one course of action (or inaction) can serve as a powerful motivator for choosing alternative actions.[412]

It may be that the source of motivation for nebuliser use shifts over the lifespan due to the accrual of experiences of aversive ill-health episodes arising from non-adherence, such that people with CF come to better understand and fear the consequences of non-adherence, which in turn stimulates adherence. Life experience may thus represent an important determinant of adherence. Encouraging young adults with better lung function to anticipate ill-health arising from not using nebulised treatments, before they actually experience such ill-health, might therefore offer a fruitful technique for them to persist with more consistent nebuliser use.

In terms of life experience with nebuliser use, it is often assumed that habits developed at a younger age will be sustained into adulthood with minimal conscious effort. However, there is actually little empirical evidence about durability of habits over time.[250] During interviews, younger participants reported that childhood experience influenced their nebuliser use but this was not the case among older participants. It may be that experience during or following the turbulent

period of late adolescence and young adulthood is more relevant for nebuliser adherence among older adults, since it is known that nebuliser adherence declined during this life stage.[194] How objective nebuliser adherence, habit and other behaviour determinants among people with CF change over time in a real-world setting requires further exploration using a longitudinal study design. However, it is clear that adherence intervention during childhood alone is unlikely to prevent low adherence in later life. Effective adherence intervention is just as important in adult CF services, especial interventions to target young adults who are most at risk for low medication adherence and poor health outcomes.

Three key findings speak to the importance of habit formation in sustaining nebuliser use. Firstly, high and low adherers notably differed in their habit strength, and in particular, the strength of tendencies to habitually instigate nebuliser use. All high adherers described, in interviews, having ‘routinised’ nebuliser use, such that they automatically ‘remember’ to use their nebulisers, and reported markedly stronger tendencies to habitually instigate nebuliser use episodes than did low adherers. This supports theoretical propositions that habit formation may maintain behaviour,[413] and empirical research suggesting habitual instigation supports frequent action.[328, 329] As habit forms, control over initially deliberative and effortful action is delegated to environmental cues, and instigating action becomes easier.[388, 405] Our data suggest that some low adherers may be stuck in the effortful early stages of habit formation, unable to develop the automaticity that sustains high adherence. Indeed, younger participants – who were typically less adherent – reported lesser habitual instigation than did older participants. Secondly, high adherers reported that habitual instigation made treatment less burdensome. Participants ‘with instigation habit’ – i.e., tending to agree that nebuliser use episodes are triggered automatically, without thinking – reported low perceived treatment burden regardless of the objective complexity of their treatment regimens. Conversely, participants ‘without instigation habit’ – i.e. tending to disagree with such statement – reported higher perceived treatment burden as treatment complexity increased. CF is a multi-system condition requiring multiple treatment types to maintain health, so requires a complex and potentially burdensome treatment regimen.[213] By automating the initiation of nebuliser use, instigation habit may reduce burden by bypassing deliberation processes.[328] Thirdly and relatedly, a moderately strong positive correlation was also found between habitual instigation of nebuliser use and perceived opportunity scores. Qualitative analysis suggested that high adherers ‘with habit’ experienced greater opportunities for nebuliser use (such as flexible working patterns), and also adapted more effectively to generate opportunities for using nebuliser when faced with challenges. It is not possible to determine the temporal relationship between opportunities and habit strength due to the cross-sectional design of this study. It may be that participants with greater opportunities were better able to form habits. Indeed, greater opportunity to act makes action more likely,[305] thus enhancing the likelihood of habit formation.[388] Alternatively, participants who form habits may have been better placed to subsequently act on opportunities, where such opportunities operated to automatically activate stored cue-behaviour

associations. The habit-opportunity relationships could also be bi-directional. Together, these findings suggest that nebuliser adherence interventions might usefully focus on habit formation. Specifically, people with CF should be encouraged to identify opportune moments in their everyday routines, and plan to respond to such moments so that nebuliser use might be consistently triggered, thus fostering habit associations.[388] Our data suggest that forming instigation habit would support adherence by not only automating nebuliser use, but also alleviating the perceived burden of using nebuliser.

Other limitations of this study must be acknowledged. The hypothesised behaviour predictors were measured via self-report. A problem inherent in any self-report survey study is careless or inattentive responding.[414] By randomly ordering the statements of the questionnaire used in the study (see Table 5.2) and including some statements that were reversely scored,[415] participants should be more attentive in providing their responses and less likely to provide identical response for consecutive statements.[415] Self-reporting habit is particularly problematic, as discussed in Section 3.4.2.6 – it has been argued that people may not reliably reflect on non-reflective processes such as habit.[334] Participants may also have been confused by the subtly different wordings of instigation and execution habit items. However, the two previous studies in this domain suggest that people can reliably discern between the concepts of habitual instigation and execution.[328, 329] Secondly, participants' familiarity with the interviewer (the PhD student) may perhaps have prompted socially desirable responses.[416] Conversely however, familiarity between the PhD student and the participants may have encouraged participants to speak more freely and openly. Indeed, between-participant variation was found on predictor variables scores, indicating that participants did not consistently self-report values to portray themselves in a positive light. Although nebuliser use was objectively measured, only the proportion of doses taken was considered in the calculation of adherence. Inadequate prescription, brief periods of nebuliser overuse or taking nebulised antibiotics with insufficient dose spacing could inflate the calculated adherence level,[182] and it is possible that a person with moderate levels of effective adherence was inadvertently labelled as a high adherer in this study. Technique errors with using nebuliser were also not considered, although I-neb® is a third generation adaptive aerosol delivery system designed to optimised technique by only releasing aerosol when an inhalation of sufficient quality is detected.[170]

Chapter 5, Section 5: Conclusions

Previous research in CF has focused predominantly on treatment burden and reflective motivation concepts such as treatment beliefs. This mixed methods study, which investigated a broader range of potential adherence predictors distinguishing high and low adherence patterns, demonstrates the importance of both reflective and automatic processes in determining adherence among adults

with CF. This is the first study which demonstrates the association between habit and objectively measured medication adherence – in previous studies investigating this association in other long-term conditions, adherence was self-reported and therefore measured with error.[7-11] This is also the first study which demonstrates the association between habitual instigation and objectively-measured health behaviour.

In addition, this study highlights the need to explore how nebuliser adherence and habit among people with CF change over time, especially during the late adolescence and young adulthood stage. Such studies would benefit from a parsimonious habit measure that can unobtrusively assess habit at various time points over prolonged periods. Longitudinal changes in objective nebuliser adherence over a 4-year period has been explored, and a pragmatic method of inferring ‘habit’ from routinely available adherence data (which allows ‘habit’ to be measured without any additional effort from adults with CF) was developed as part of the PhD research, but these are beyond the scope of this thesis.

Due to the preliminary and exploratory nature of this mixed methods study, our findings do require replication among larger samples to reduce the uncertainty of evidence – hence the study that is reported in the next chapter (Chapter 6). Nonetheless, the findings suggest that nebuliser adherence interventions for adults with CF might usefully target the development of routines to instigate nebuliser use, identify opportune moments for using nebuliser, and utilise anticipated regret as a technique to support asymptomatic low adherers, especially among younger adults with good lung function.

CHAPTER 6: A SECONDARY QUANTITATIVE DATA ANALYSIS TO REPLICATE SOME OF THE FINDINGS IN CHAPTER 5

Chapter 6, Section 1: Introduction

Replication studies are studies that re-perform previous experiments or analyses to determine if consistent results were reached.[417] These type of studies, though they may be dismissed as lacking originality or innovation, are important for scientific progress by reducing the uncertainty of evidence and confirming the validity of scientific conclusions.[418] Since the publication of a provocative essay by Ioannidis in 2005 which claims that “most published research findings are false”,[419] there have been several high-profile projects that showed high rates of replication failure in a broad range of subjects including social science, economics, clinical research and psychology.[420-423] In this context, the mixed methods study reported in Chapter 5 requires replication due to the small sample size and the findings within a single cohort may not be generalisable.

The ACTiF pilot (ISRCTN ISRCTN13076797) provides an opportunity for replication because nebuliser adherence were also objectively measured using electronic data capture (EDC) and a broad range of potential adherence predictors were measured at baseline (prior to the delivery of any intervention). The ACTiF pilot is a two-centre external pilot trial primarily designed to evaluate the feasibility of a full-scale nebuliser adherence intervention RCT (CFHH RCT, ISRCTN55504164). The ACTiF pilot recruited 64 participants and randomised 32 participants to CFHealthHub, a software platform which delivers a complex intervention to support habit formation and self-management with inhaled therapies among adults with CF. The other 32 participants were randomised to usual care.

Some of the potential adherence predictors collected during the ACTiF pilot were similar to the potential predictors collected during the mixed methods study reported in Chapter 5. These were treatment burden (treatment complexity and perceived treatment burden), instigation habit and intention. Other potential adherence predictors collected during the ACTiF pilot included severity of anxiety, severity of depressive disorder and beliefs about treatment (which is a component of reflective motivation).

Although anxiety and depression have been hypothesised to reduce adherence, the evidence for this is inconclusive. A recent study found that the effect of depressive symptoms on medication adherence was mediated by ‘medication beliefs’ (see Sections 3.3.7 and 3.3.10).[290] Two previous studies using the Beliefs about Medication Questionnaire (BMQ) to evaluate treatment

beliefs found that lower treatment adherence was associated with necessity beliefs rather than concerns beliefs (Section 3.3.7).[277, 278] Of note, adherence were not objectively measured in both those studies; hence the association between adherence and treatment beliefs among people with CF remains uncertain.

This chapter therefore sets out to replicate two of the main findings from mixed methods study reported in Chapter 5 (i.e. habit is associated with nebuliser adherence and habit has the potential to attenuate perceived treatment burden) by performing secondary quantitative analysis using data from ACTiF pilot. The third main finding from the mixed methods study (i.e. positive correlation between habit scores and perceived opportunity) could not be replicated, since opportunity score was not collected during ACTiF pilot. In addition, this chapter also sets out to explore the potential effects of anxiety, depressive disorder and treatment beliefs on nebuliser adherence.

Chapter 6, Section 2: Methods

6.2.1 Setting and participants

This is a secondary quantitative analysis using data prospectively collected during the ACTiF pilot. The ACTiF pilot was approved by the London – Brent Research Ethics Committee (REC reference: 16/LO/0356).

Of the 64 participants recruited during ACTiF pilot, three participants were excluded because a participant withdrew consent, a participant died during the pilot and a participant did not provide data for potential adherence predictors at baseline. All included participants were aged ≥ 16 years, diagnosed as having CF according to the UK CF Trust criteria [348] and were using preventative inhaled therapies as part of their routine treatment. Participants were recruited from the Wolfson CF Centre ($N = 29$) and the Wessex Adult CF Centre ($N = 32$) from June to September 2016.

6.2.2 Measures

6.2.2.1 Demographic data and health outcomes

Demographic and health outcomes data e.g. age, gender, %FEV₁, intravenous (IV) antibiotics use and quality of life were collected as part of the trial procedure during the baseline visit.

Baseline %FEV₁ data were collected at the time of recruitment. FEV₁ was measured during a period of clinical stability and %FEV₁ was calculated using the Global Lung Function Initiative (GLI) equation.[354]

Severity and frequency of *pulmonary exacerbations* were captured via total IV antibiotic days over the 1-year period prior to recruitment, and for 6 months during the ACtiF pilot.

Quality of life at baseline was self-reported on a 1 ('a great deal') to 4 ('not at all') scale using all six relevant items from the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain,[395] e.g. 'Have you been coughing during the day?'; $\alpha = 0.90$. The respiratory domain of CFQ-R score was calculated from the six relevant CFQ-R items using previously described methods,[395] and ranged from 0 (lowest quality of life) to 100 (highest quality of life).

6.2.2.2 Nebuliser adherence

Objective nebuliser data were downloaded from chipped nebulisers (eTrack®) in the 3-month period following the point of recruitment. The implementation phase of adherence was calculated as a percentage between total amount of medications used against the agreed dose between clinicians and adults with CF. Based on this method of quantifying adherence, adherence levels can vary from 0% to >100% (due to potential nebuliser overuse), with higher adherence being more desirable although nebuliser adherence >100% may not be optimum (this may vary with the medications – hypertonic saline may be beneficial if used more frequently whereas antibiotics may cause toxicity if used substantially more frequently than the prescribed doses).

6.2.2.3 Hypothesised predictors of adherence

Treatment burden was measured in two ways. 'Objective' burden was measured via the Treatment Complexity Score (TCS),[213] which assigns a value of 1, 2 or 3 (3 = highest burden) to the 37 CF maintenance therapies. The individual values were summed up to produce a single TCS score ranging from 0 (no burden) to 72 (highest burden). 'Subjective' burden was self-reported on a 1 ('not at all') to 4 ('a lot') scale using all three relevant items from the CF Questionnaire-Revised (CFQ-R),[395] e.g. "To what extent do your treatments make your daily life more difficult?"; $\alpha = 0.45$. 'Subjective' burden score was calculated from the three relevant CFQ-R items using previously described methods,[395] and ranged from 0 (lowest perceived burden) to 100 (highest perceived burden).

Severity of anxiety at baseline was self-reported on a 0 ('not at all') to 3 ('nearly every day') scale using all seven items from the General Anxiety Disorder 7-item anxiety scale (GAD),[424] e.g. "Feeling nervous, anxious or on edge"; $\alpha = 0.83$. All seven GAD items were summed to create an anxiety score ranging from 0 (lowest anxiety severity) to 21 (most severe anxiety).

Severity of depressive disorder at baseline was self-reported on a 0 ('not at all') to 3 ('nearly every day') scale using all eight items from the Patient Health Questionnaire depression scale (PHQ-8),[425] e.g. "Little interest or pleasure in doing things"; $\alpha = 0.84$. All eight PHQ-8 items were summed to create a depressive disorder score ranging from 0 (lowest depressive disorder severity) to 24 (most severe depressive disorder).

Intention at baseline was self-reported using an item adapted from the Capability Opportunity Motivation Behaviour (COM-B) Self Evaluation Questionnaire.[398] The item used was “I want to do all my prescribed nebuliser treatments in the next two weeks” with which participants rate agreement on a scale of 1–7, where 7 represents strongest intention.

Necessity at baseline was self-reported on a 1 (‘strongly disagree’) to 5 (‘strongly agree’) scale using all seven ‘necessity items’ from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ),[426] e.g. “My life would be impossible without this nebuliser treatment”; $\alpha = 0.84$. All seven ‘necessity items’ from the BMQ were averaged to create a necessity score ranging from 1 (lowest perceived necessity) to 5 (highest perceived necessity).

Concerns at baseline was self-reported on a 1 (‘strongly disagree’) to 5 (‘strongly agree’) scale using all 14 ‘concern items’ from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ),[426] e.g. “I sometimes worry about becoming too dependent on this nebuliser”; $\alpha = 0.84$. All 14 ‘concern items’ from the BMQ were averaged to create a concerns score ranging from 1 (lowest perceived concern) to 5 (highest perceived concern).

Habit strength at baseline was self-reported on a 1 (‘strongly disagree’) to 5 (‘strongly agree’) scale using all four items from the Self-Report Behavioural Automaticity Index (SRBAI),[336] e.g. “deciding to use my nebuliser is something I do automatically”; $\alpha = 0.93$. Each item begins with “Deciding to use my nebuliser ...” to capture habitual instigation, since the mixed methods study reported in Chapter 5 suggested that effects of non-specific habit on adherence may be more precisely attributed to habitual instigation. Other studies have also demonstrated that habitual instigation tendency is more likely to predict behaviour frequency, compared to habitual execution tendency.[328, 329] Only habitual instigation was measured to minimise participant burden, especially since the CFQ-R questionnaire alone consists of 50 items.[395] All four SRBAI items were summed to create a habit strength score ranging from 4 (weakest habit) to 20 (strongest habit).

6.2.3 Analysis

All analyses were run using SPSS v24 (IBM Corp) and R v3.3.0 (www.r-project.org). Appropriate descriptive statistics were generated, including effect sizes and confidence intervals. P-values <0.05 were considered statistically significant.

6.2.3.1 Exploring the potential effects of hypothesised adherence predictors on adherence

Characteristics of ‘high’ (adherence $\geq 80\%$), ‘moderate’ (adherence 50-79.9%) and ‘low’ (adherence <50%) adherers were compared, to mirror the analysis of the mixed methods study reported in Chapter 5. These adherence categories were also used in various other CF adherence-related

studies [200, 283] and were chosen based on the relationship with health outcomes. For example, a previous study found that adults with adherence $\geq 80\%$ had total annual healthcare costs of \$34,432; whereas those with adherence 50-79.9% and $< 50\%$ had costs of \$45,239 and \$54,190, respectively.[283]

Due to the non-normal data distribution and the presence of outliers, non-parametric analysis methods were used. Again, this mirrors the quantitative analysis method used for the mixed methods study reported in Chapter 5. If two or more hypothesised adherence predictors were significantly associated with adherence, multiple ordinal regression would be performed using the relevant hypothesised adherence predictors as fixed effects and the three adherence categories as the dependent variable.

6.2.3.2 Exploring whether habit attenuated perceived treatment burden

For this analysis, the sample was dichotomised into those who 'had habit' (i.e. high level of automaticity, habit score ≥ 12 , that is, at or above the scale midpoint [405]) or 'had no habit' (habit score < 12) to explore whether relationships between treatment complexity and perceived burden differed according to the presence or absence of habit. This is similar to the analysis of the mixed methods study reported in Chapter 5.

Of note, the Cronbach's alpha for perceived treatment burden was only 0.45 whilst the values were > 0.80 for all other self-reported measures. Although a high Cronbach's alpha value does not imply the measure is unidimensional,[342] such a low value indicates a lack of internal consistency. All three perceived treatment burden items were retained for the main analysis as described in Section 6.2.3.1; but the perceived treatment burden measure was further explored to determine whether the two items deemed to have the best face validity ("To what extent do your treatments make your daily life more difficult?" and "How difficult is it for you to do your treatments, including medications, each day?") differed from the third statement ("How much time do you currently spend each day on your treatments?"). The first two items, but *not* the third item, were used to measure perceived treatment burden in the mixed methods study reported in Chapter 5.

Chapter 6, Section 3: Results

This analysis included 61 adults (28, 45.9% were females). The overall baseline adherence level was low, with median 38.5% (IQR 7.4% to 66.3%) and most participants ($N = 40$, 65.6%) had adherence $< 50\%$. High adherers ($N = 9$, 14.8%) had lower prior-year IV use and tended to have higher %FEV₁ at baseline, see Table 6.1.

Table 6.1: Clinical characteristics and psychological factors among three groups of adults with CF in the ACTiF pilot, stratified according to three categories of adherence

	Low adherence, i.e. <50% <i>N</i> = 40	Moderate adherence, i.e. 50–79.9% <i>N</i> = 12	High adherence, i.e. ≥80% <i>N</i> = 9	P-value †
% Adherence, median (IQR)	13.5 (5.1 – 38.1)	66.3 (54.8 – 77.5)	92.5 (82.4 – 97.4)	
<u>Clinical characteristics:</u>				
Age in years, median (IQR)	27.4 (21.8 – 37.0)	24.5 (18.4 – 36.3)	26.1 (20.5 – 35.3)	0.750
Female, n (%)	20 (50.0)	6 (50.0)	2 (22.2)	0.334
Baseline %FEV ₁ , median (IQR)	51.2 (43.6 – 68.0)	47.7 (42.8 – 90.1)	79.7 (51.1 – 89.7)	0.176
Prior-year IV days, median (IQR)	28 (11 – 46)	17 (14 – 55)	0 (0 – 12)	0.016
IV days during trial, median (IQR)	14 (0 – 23)	17 (0 – 31)	0 (0 – 15)	0.225
Quality of life (CFQ-R), median (IQR)	56 (33 – 78)	47 (28 – 79)	67 (42 – 86)	0.525
Treatment complexity (TCS), median (IQR)	15 (12 – 18)	16 (12 – 18)	13 (10 – 18)	0.562
<u>Psychological factors:</u>				
Perceived burden (CFQ-R), median (IQR)	44 (33 – 56)	56 (44 – 67)	44 (33 – 56)	0.546
Anxiety (GAD) score, median (IQR)	4 (1 – 8)	2 (0 – 5)	0 (0 – 4)	0.121
Depression (PHQ-8) score, median (IQR)	7 (3 – 12)	5 (3 – 8)	4 (2 – 5)	0.227
Intention (COM-B) score, median (IQR)	7 (5 – 7)	7 (7 – 7)	7 (6 – 7)	0.076
Necessity (BMQ) score, median (IQR)	3.1 (2.8 – 3.7)	3.2 (2.7 – 3.7)	4.0 (2.9 – 4.6)	0.178
Concerns (BMQ) score,[‡] median (IQR)	2.3 (1.9 – 2.6)	2.2 (1.5 – 2.6)	1.5 (1.3 – 1.7)	0.009
Habit (SRBAI) scores,[‡] median (IQR)	8.0 (4.0 – 10.0)	14.5 (12.0 – 17.5)	18.0 (13.0 – 19.5)	< 0.001
<u>Results from the mixed methods Sheffield study (reported in Chapter 5) included for comparison</u>				
Number of participants [¶]	10	0	10	
% Adherence, median (IQR)	28.0 (5.3 – 46.0)	N/A	94.9 (86.7 – 108.5)	
Habit (SRBAI) scores, [¶] median (IQR)	9.7 (7.2 – 12.0)	N/A	16.3 (13.0 – 18.2)	0.002

† All p-values were calculated using Kruskal-Wallis H test, except the p-value for gender was calculated using Fisher's exact test.

‡ Since concerns and habit scores were associated with adherence, both scores were included as covariates in a multiple ordinal regression model with adherence categories as the dependent variable (see Table 6.2 for the results of the ordinal regression analysis).

¶ By design, the mixed methods study reported in Chapter 5 only included adults with adherence <50% or ≥80%.

¶ In the mixed methods study reported in Chapter 5, habit (SRBAI) scores were collected using a 1–7 Likert scale. For the purpose of this comparison, the score of each Sheffield participant was transformed linearly to a 4–20 scale, to mirror the scoring system used in the ACTiF pilot.

6.3.1 The relationship between hypothesised adherence predictors and adherence

High adherers (*N* = 9) reported stronger habit (median 18.0, IQR 13.0 to 19.5) than did low adherers (*N* = 40; median 8.0, IQR 4.0 to 10.0), see Table 6.1. Conversely, high adherers reported lower concerns (median 1.6, IQR 1.3 to 1.7) than did low adherers (median 2.3, IQR 1.9 to 2.6).

In a multiple ordinal regression model with both habit and concerns scores (see Table 6.2), only habit was independently associated with adherence – the adjusted odds ratio indicates that 1 unit increase in habit score (which can vary from 4, weakest habit to 20, strongest habit) was associated with an increase in the odds of moving up one level of adherence category (e.g. from <50% to 50–79.9%, or 50–79.9% to ≥80%) by 39% (95% CI 19% to 62%), once concerns score was taken into account.

Table 6.2: Summary of the multiple ordinal regression model[§] with the three adherence categories (<50%, 50–79.9%, ≥80%) as the dependent variable

Variable	Adjusted odds ratio (95% CI)	P-value
Concerns (BMQ) score	0.35 (0.11 to 1.06)	0.062
Habit (SRBAI) score^Δ	1.39 (1.19 to 1.62)^Ω	< 0.001

[§] For this ordinal regression model: pseudo- $R^2 = 0.505$ (Nagelkerke); model $\chi^2 (2) = 33.0$, $p < 0.001$. This suggests that 50.5% of the variance in the adherence categories were explained by concerns and habit scores.

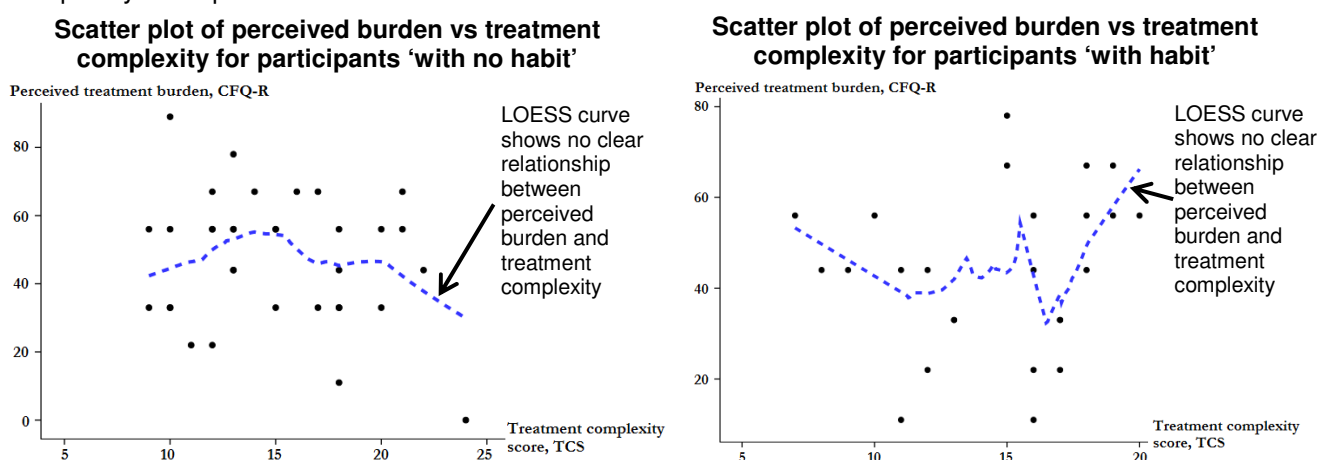
^Δ An adjusted odds ratio of 1.39 indicates an increase in 1 unit of habit score (which can vary from 4, weakest habit to 20, strongest habit) was associated with an increase in the odds of moving up one level of adherence category (e.g. from <50% to 50–79.9%, or 50–79.9% to ≥80%) by 39% (95% CI 19 to 62%), once concerns score was taken into account.

^Ω The different scales used for habit and concerns scores meant that it is difficult to directly compare effect sizes for these two covariates. The scales can be 'standardised' by averaging the four SRBAI items to calculate the habit score, which would create a habit strength score ranging from 1 (weakest habit) to 5 (strongest habit). This is directly comparable to the concerns score, which ranged from 1 (lowest perceived concern) to 5 (highest perceived concern). Using the 'standardised habit score' and the concerns score as fixed effects covariates in the multiple ordinal regression model, the adjusted odds ratio for habit score = 3.71 (95% CI 2.01 to 6.82). This indicates a greater effect size for habit score – a 1 unit increase in habit score was associated with an increase in the odds of moving up one level of adherence category by 271% whereas a 1 unit decrease in concerns score was associated with an increase in the odds of moving up one level of adherence category by 65%.

6.3.2 The potential attenuation of perceived treatment burden by habit

Both scatter plots for participants 'with no habit' ($N = 34$) and 'with habit' ($N = 27$) showed no linear relationship between perceived treatment burden and treatment complexity, see Figure 6.1.

Figure 6.1: Local Polynomial Regression (LOESS) curves[§] depicting the relationship between treatment complexity[†] and perceived treatment burden[‡]



[§] Local Polynomial Regression (LOESS) curve is a non-parametric method for fitting smooth curves to empirical data, to depict the relationships between variables.[427] Both LOESS curves were generated using default SPSS v24.0 setting (Kernel: Epanechnikov, 50% of points to fit).

[†] Treatment complexity score can vary from 0 to 72, with higher scores indicating more complex treatment regimen [213]

[‡] Perceived treatment burden as measured using CFQ-R can vary from 0 to 100, with higher scores indicating higher perceived treatment burden [395]

The Spearman's rho also showed no clear linear relationship between perceived burden and treatment complexity for participants 'with no habit' ($r = -0.09$, 95% CI -0.42 to 0.25) and 'with habit' ($r = 0.21$, 95% CI -0.18 to 0.55) since the 95% confidence intervals included the value of zero.

6.3.3 Further exploration of the perceived burden score (and treatment complexity score)

For reporting purposes, the item "To what extent do your treatments make your daily life more difficult?" was denoted as Statement 1 (S1); "How much time do you currently spend each day on your treatments?" as Statement 2 (S2) and "How difficult is it for you to do your treatments (including medications) each day?" as Statement 3 (S3).

The Cronbach's alpha for S1-S2, S2-S3 and S1-S3 pairs were 0.35, -0.12 and 0.64 respectively. This finding is unlikely to be a fluke or due to inappropriate use of the CFQ-R questionnaire. In the original 2005 validation study for CFQ-R, the S1-S2 pair had Cronbach's alpha of only 0.18; hence a third item (S3) was added in an attempt to improve the scale-level reliability.[395] The psychometric properties of CFQ-R was re-evaluated among 4,679 teenagers and adults as part of the Epidemiologic Study of Cystic Fibrosis (ESCF) in 2012, yet the Cronbach's alpha for the 3-item burden domain was only 0.51 – the perceived burden domain still has the lowest Cronbach's alpha among all 13 domains of the CFQ-R.[428]

This suggests that S2 may be measuring a different dimension from S1 and S3, i.e. how much time an adult with CF spend on treatment may not necessarily correlate with how burdensome that person finds the treatment regimen. However, generating a perceived burden score based only on S1 and S3 still found no clear linear relationship between perceived burden and treatment complexity for participants 'with no habit' ($r = -0.24$, 95% CI -0.54 to 0.10) and 'with habit' ($r = 0.22$, 95% CI -0.18 to 0.55).

At a group level, the Sheffield participants of the mixed methods study reported in Chapter 5 had less severe disease as evidenced by higher %FEV₁ (even after accounting for the differences in measurement methods) and lower proportion of people with CF related diabetes, see Table 6.3. The adherence levels were higher in the Sheffield mixed methods study, due to the purposive nature of sampling for the mixed methods study which requires equal numbers of high vs low adherers. Given the higher adherence in the mixed methods study and the strong habit-adherence association observed in Chapter 5, it is not surprising that participants in the mixed methods study also reported stronger habit. However, the perceived burden was substantially higher among participants of the ACtiF pilot, even though treatment complexity scores among both cohorts of participants were similar. It is also surprising that the treatment complexity scores were similar among both cohorts of participants, since participants of the ACtiF pilot clearly had more severe lung disease (which would be expected to increase the complexity of treatment regimen) and higher prevalence of CF related diabetes (which is typically managed with insulin).

Table 6.3: The comparison between two cohorts of participants

	Mixed methods study (<i>N</i> = 20)	ACtiF pilot (<i>N</i> = 61)
Age in years, median (IQR)	27 (19 to 32)	27 (21 to 50)
% predicted FEV₁ , median (IQR)	83.5 (69.0 to 90.8) ^a	52.8 (43.3 to 78.9) ^b
CF related diabetes , n (%)	4 (20.0%)	25 (41.0%)
% Adherence , median (IQR)	61.5 (26.7 to 95.0) [†]	38.5 (7.4 to 66.3)
Low adherence, n (%)	10 (50.0%)	40 (65.6%)
Moderate adherence, n (%)	0	12 (19.7%)
High adherence, n (%)	10 (50.0%)	9 (14.8%)
Habit score, median (IQR)	12.0 (8.8 to 16.5) [‡]	10.0 (6.5 to 15.0)
Perceived treatment burden , median (IQR)	16.7 (0.0 to 41.7) [¶]	44.0 (33.0 to 56.0) [§] 50.0 (25.0 to 66.7) ^Ω
Treatment complexity score , median (IQR)	15.0 (10.3 to 16.0)	15.0 (12.0 to 18.0)

^a %FEV₁ for the mixed methods study participants were the best %FEV₁ in the previous 12 months prior to recruitment, as calculated using the Knudson equation.[394]

^b %FEV₁ for the ACtiF pilot participants were stable %FEV₁ at baseline, as calculated using the Global Lung Function Initiative (GLI) equation.[354]

[†] This group level figure is only a guide because there were two distinct adherence groups in the Sheffield cohort.

[‡] In the mixed methods study reported in Chapter 5, habit (SRBAI) scores were collected using a 1–7 Likert scale. For the purpose of this comparison, the score of each Sheffield participant was transformed linearly to a 4–20 scale, to mirror the scoring system used in the ACtiF pilot.

[¶] In the mixed methods study reported in Chapter 5, perceived treatment burden (CFQ-R) scores were collected using a 1–7 Likert scale. For the purpose of this comparison, the score of each Sheffield participant was transformed linearly to a 0–100 scale, to mirror the scoring system used in the ACtiF pilot.

[§] This score was calculated using all three relevant items from the CFQ-R.

^Ω This score was calculated using two items from the CFQ-R: “To what extent do your treatments make your daily life more difficult?” and “How difficult is it for you to do your treatments (including medications) each day?”. This was similar the method of measuring perceived treatment burden in the mixed methods study reported in Chapter 5.

Chapter 6, Section 4: Discussion

Secondary analysis of the ACtiF pilot data has replicated the habit-adherence association finding from the Sheffield mixed methods study reported in Chapter 5. In the mixed methods study, adherence was assessed *retrospectively* in the 1-year pre-recruitment period. In the secondary analysis of ACtiF pilot data, adherence was assessed *prospectively* over the 3-month post recruitment period in the study. Adherence data was analysed over the 3-month post recruitment period because baseline objective adherence data (i.e. prior to adherence intervention) was unavailable, sampling adherence over shorter periods is an unreliable measure of stable behaviour [181] and adherence levels were similar in both arms of the pilot for the first three months (median 38.5%, IQR 8.7% to 71.8% for intervention, *N* = 33; median 37.9%, IQR 5.5% to 54.6% for usual care, *N* = 28). Sampling adherence over a 6-month post recruitment period would be complicated by the divergence in adherence at month 4–6 (median 33.7%, IQR 7.2% to 75.0% for intervention, *N* = 31; median 21.2%, IQR 7.0% to 55.9% for usual care, *N* = 27). This trend of declining

adherence levels among ACtiF pilot participants from month 1–3 to month 4–6 also reiterates the finding in Chapter 4 that adherence to longer-term treatment regimen is lower than shorter-term regimen.

Although the group-level habit scores were higher for the Sheffield mixed methods study cohort, the scores were similar between both cohorts following stratification according to adherence levels. This suggests that habit – that is automatically experiencing an urge to use the nebuliser in certain settings, due to learned associations between nebuliser use and cues within those settings – may be consistently associated with nebuliser adherence among adults with CF.

Due to the cross-sectional nature of the data, the directionality of the association between habit and adherence cannot be determined for certain. The relationship between adherence and habit over time is complex; initial adherence episodes (undertaken in consistent settings) cause habit to form, and as habit forms, it acquires the potential to direct subsequent adherence.[250] While the habit scores analysed were collected at baseline, prior to the delivery of any intervention during the ACtiF pilot, the detailed data on participants' adherence (or intervention) histories were unavailable. It may be possible that some of the participants to have been “successfully intervened upon” in the past, and so may have achieved higher adherence prior to entering the study, and maintained these throughout the study. Assuming stability of adherence and habit over time, high adherence prior to entering the study may have caused higher habit scores at baseline, which then subsequently predicted (in a statistical sense) higher adherence over the following three months.

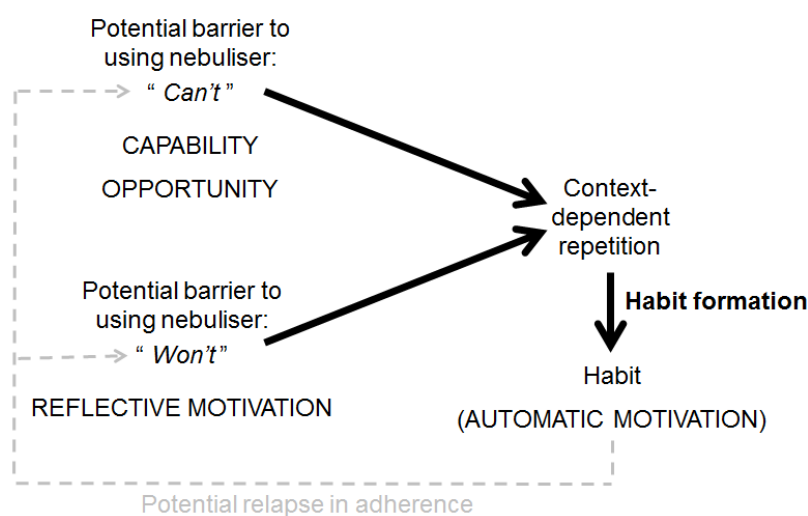
The habit measure used for both the Sheffield mixed methods study and the ACtiF pilot is the SRBAI, which is an automaticity subscale of the SRHI (see Sections 3.4.2.2 and 3.4.2.3 for detailed explanation about both habit measures). Unlike SRHI, SRBAI does not enquire about behaviour frequency.[336] It means that SRBAI scores are less likely to be just acting as proxy measures for behaviour frequencies. Although changing adherence could potentially change habit (since habit is strengthened through consistent repetition of a specific action in a specific context, i.e. content-dependent repetition),[250] it is important to note that habit is not synonymous with behaviour (e.g. adherence). It is possible that someone using his or her nebuliser frequently to have weak habit if he or she does not use the nebuliser in a consistent setting, and instead rely on consciously remembering to use the nebuliser. It is also, in theory, possible to strengthen habit without directly increasing the frequency of nebuliser use, by instead encouraging more consistent performance.[388] For example, adults with CF might be encouraged to identify cues that they encounter reliably and regularly in everyday routines, in the presence of which they should use their nebuliser.[314] Such habit-based advice would therefore focus on harnessing potential contextual cues, not increasing the frequency of nebuliser use per se.

Although habit was found to be the only independent predictor of nebuliser adherence in the ACtiF pilot cohort, this is not to say that habit is the only relevant determinant of adherence. Due to

modest sample size, the ACtiF pilot could only detect differences if the effect size is sufficiently large.[232] For example, a 1 unit decrease in concerns score (concerns score could vary from 1, lowest perceived concern to 5, highest perceived concern) could be associated with an increase in the odds of moving up one level of adherence category (e.g. from <50% to 50–79.9%, or 50–79.9% to ≥80%) by 65% but the ACtiF pilot was not sufficiently powered to detect that effect with a conventional α level of 0.05.

It is likely that both reflective (e.g. treatment beliefs) and automatic (e.g. habit) processes influence adherence levels, which would be detected with larger sample sizes. In particular, reflective motivation is crucial in the early stages of habit formation because reflective motivation is important for a person to start repeating the behaviour in a specific context (i.e. context-dependent repetition) to strengthen the context-behaviour association. The initial process of habit formation is effortful.[314] Barriers to the behaviour must be overcome to initiate context-dependent repetition. Conscious attention or reflective processes are also needed to persist with context-dependent repetition (see Figure 6.2).[250, 314, 398]

Figure 6.2: The process of habit formation in nebuliser adherence (modified from Figure 1.5 of reference [398])



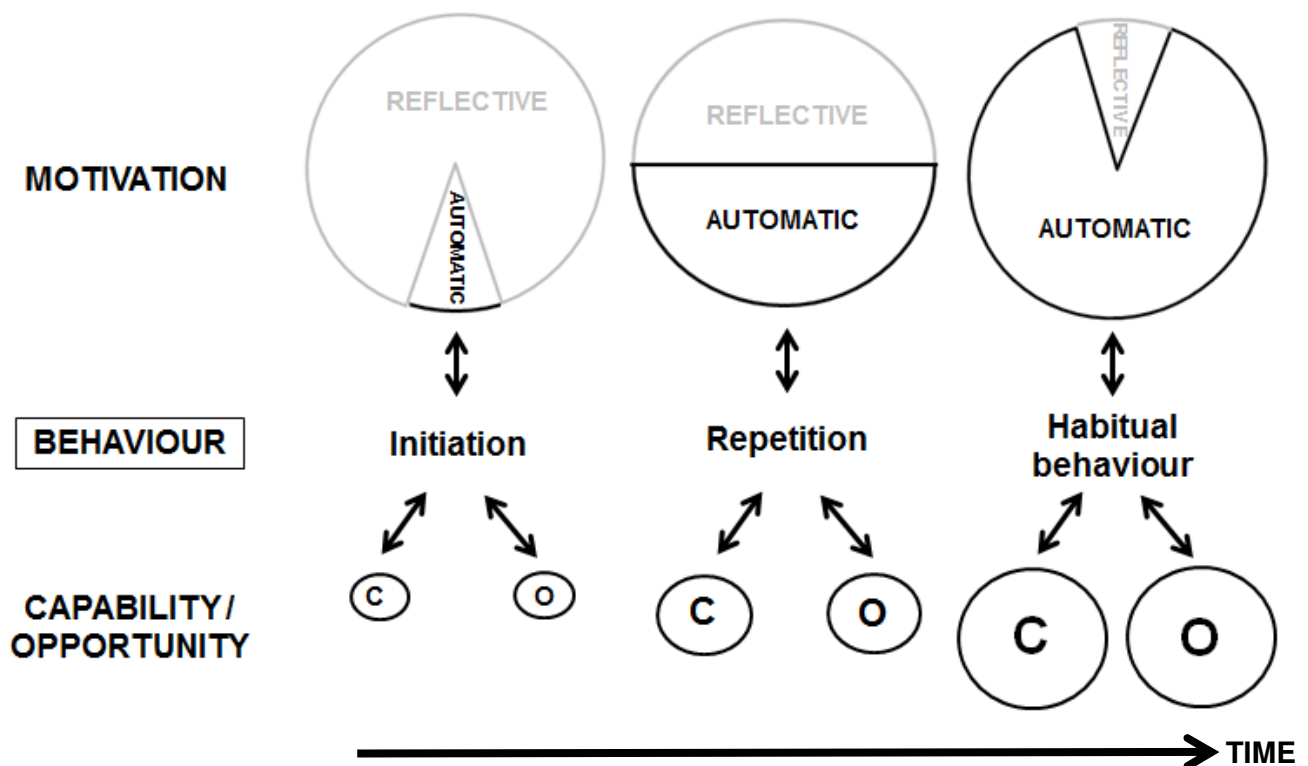
The Perceptions and Practicalities Approach (PAPA) proposes that non-adherence can be unintentional (“can’t”), arising from practical barriers (e.g. lack of time) or intentional (“won’t”), arising from attitudinal barriers (e.g. lack of necessity, overwhelming concerns).[429] Within the COM-B model (Capability, Opportunity, Motivation and Behaviour), those who “can’t” adhere lack capability and/or opportunity, whilst those who “won’t” adhere lack motivation.[398]

Overcoming these barriers allows context-dependent repetition. Context-dependent repetition gradually shifts the cognitive control of a behaviour from reflective to automatic processes, i.e. the process of habit formation. Habit should sustain a behaviour but disruption of habitual behaviour is possible, e.g. discontinuation of cue exposure with alteration of the environment. If adherence has relapsed, it is important to overcome barriers to start habit formation again.

However, working effortfully on a new behaviour (e.g. using nebuliser) is worthwhile if it results in habitual behaviour. The gradual shifting of a behaviour’s cognitive control from reflective to automatic processes means that as habit develops, it can cue further context-dependent

repetitions which in turn further strengthens the habit.[250] Behaviour enactment becomes progressively easier with this positive feedback loop, even though the initial process of habit formation is effortful.[314] Other components of COM-B model also interact and change over time during the process of habit formation (see Figure 6.3),[398] which highlight the theoretical potential of habit formation to sustain behaviour change.

Figure 6.3: Interaction of COM-B components during habit formation (modified from Figure 1.6 of reference [398])



The increasing ratio of automatic vs reflective motivation over time depicts the gradual shifting of a behaviour's cognitive control from reflective to automatic processes as habit is formed.

The increasing size of the 'capability' and 'opportunity' circles over time depicts increasing capability and opportunities as habit is formed. This is in keeping with the Sheffield mixed methods study reported in Chapter 5, which found a strong positive correlation between habit scores and perceived opportunity. The qualitative data of the mixed methods study suggested that those with high habit not only experienced more opportunities, but they also adapted more effectively to seize opportunities for using nebuliser.

Replication of the Sheffield mixed methods study finding in an independent cohort nonetheless provides empirical evidence that the habit-adherence association is potentially generalisable among adults with CF. The modest sample size for both studies is a limitation, but studies with larger sample sizes could still find that habit has a stronger effect on nebuliser adherence compared to other adherence determinants. There is only one previously published study examining the association between respiratory medication adherence and habit strength. The study among 139 asthma patients also found that medication adherence was more strongly associated with habit strength compared to other psychological factors such as self-efficacy and attitude.[11]

Two findings from the ACtiF pilot hinted that adults with CF may not necessarily equate greater length of time spent time on treatment or greater complexity of treatment regimen as “more difficult”. First, the item “How much time do you currently spend each day on your treatments?” was not internally consistent with the two other CFQ-R treatment burden items (“To what extent do your treatments make your daily life more difficult?” and “How difficult is it for you to do your treatments, including medications, each day?”). Second, there was a lack of relationship between treatment complexity and perceived burden among participants of the ACtiF pilot.

However, there was no clear evidence of habit moderating perceived treatment burden within the ACtiF pilot cohort. Four differences between the mixed methods study and ACtiF pilot may explain the non-replication of the ‘habit moderating treatment burden’ result. First, the measure for perceived treatment burden in the ACtiF pilot using all three relevant items from the CFQ-R appeared to lack internal consistency with $\alpha = 0.45$. The Cronbach’s alpha improved to 0.64 by using just two out of the three relevant items from CFQ-R with the best face validity (both these statements were used to measure perceived treatment burden in the mixed methods study), but there was still no clear relationship between perceived treatment burden and treatment complexity. This suggests that the perceived burden measure may contribute to, but is not the only reason for the non-replication of the results. Second, less accurate treatment complexity scores from the ACtiF pilot could potentially obscure the moderating influence of habit on perceived treatment burden. The ACtiF pilot cohort has more severe lung disease and higher prevalence of CF related diabetes compared to the mixed methods study cohort, yet treatment complexity was similar for both cohorts. CF related diabetes is typically treated with insulin,[355, 361-363] which scores a “3” on the Treatment Complexity Score [213] and should have a substantial impact on a cohort with median treatment complexity score of only 15. Prescription data for the mixed methods study were collected by a clinician who carefully checked all the prescription details. The interventionists in ACtiF pilot who collected the data could only rely on prescription records, which may or may not be accurate. Third, participants of the mixed methods study were fed back their objective nebuliser adherence data prior to completing the questionnaires (which included measure for perceived treatment burden). Participants of the ACtiF pilot could potentially be “less well calibrated” since objective nebuliser data was unavailable prior to that study. This could potentially influence the results, although it is uncertain whether better calibration to a behaviour (adherence) would confer better calibration to a psychological factor (e.g. perceived treatment burden). Fourth, there may be inherent differences in the characteristics between the two cohorts. The ACtiF pilot cohort reported similar levels of anxiety compared to the UK adult CF population (8/61, 13.1% of the ACtiF pilot cohort reported moderate-severe anxiety as measured by GAD score of ≥ 10 , which is roughly equivalent to HAD score ≥ 11 for anxiety items; ~13% of the adults with CF in the UK reported HAD score ≥ 11 for anxiety items according to the large study by Duff et al [284]). However, moderate-severe depression was much more common among the participants of ACtiF pilot (18/61, 29.5% of the ACtiF pilot cohort reported moderate-severe depression as measured by PHQ-8 score of ≥ 10 ,

which is roughly equivalent to HAD score ≥ 11 for depression items;[430] only ~4% of the adults with CF in the UK reported HAD score ≥ 11 for depression items according to the large study by Duff et al [284]). These GAD and PHQ-8 readings were taken at baseline and thus unrelated to the research procedures or intervention delivery during the pilot. The high levels of depression may partly explain the substantially higher perceived treatment burden among participants of ACtiF pilot in comparison to the participants of the mixed methods study, although it should be noted that a previous study found no correlation between depression and perceived treatment burden,[288] and participants of ACtiF pilot also reported lower habit scores compared to participants in the Sheffield mixed methods study

Chapter 6, Section 5: Conclusions

Despite the limitations of both the Sheffield mixed methods study and the secondary analysis of ACtiF pilot data, replication of the habit-adherence association suggests this association is not just a peculiarity specific to a single adult CF centre. Replication of results reduces the uncertainty of evidence, hence these studies provide tentative evidence for the role of habit in the health behaviour of using nebuliser among adults with CF. This finding is particularly pertinent in the context of difficulties with sustaining longer-term nebuliser adherence among adults with CF.

Although the finding from the Sheffield mixed methods study that habit can potentially moderate perceived treatment burden was not replicated, the non-replication may be related to limitations of the ACtiF pilot data rather than the initial finding being spurious. Given the paucity of habit-related research in respiratory medication adherence, further investigation of habit as an adherence determinant, the mechanism of habit in sustaining long-term adherence and habit-formation as a potential adherence intervention should be seen as a priority within cystic fibrosis and other areas of respiratory medicine.

Two further studies are now underway to explore habit formation in more detail using CFHealthHub in a 19-centre RCT (ISRCTN55504164) and a three-centre improvement collaborative (ISRCTN14464661). These studies should extend our understanding of the role of habit in sustained behaviour change among adults with CF.

CHAPTER 7: DISCUSSION & CONCLUSIONS

This chapter summarises the overall findings of the thesis, explains the context of the findings in relation to other research work of the PhD, discusses the relevant learning points, and provides suggestions for future research.

Chapter 7, Section 1: A summary of the findings

The aims of the thesis are to explore the clinical and psychological factors associated with objective nebuliser adherence among adults with CF.

The literature review in Chapter 3 highlighted the paucity of research using objective adherence data to understand nebuliser adherence among people with CF. The extant literature in CF adherence has also mainly focused on presumed barriers to treatment (especially “treatment burden”) and conscious deliberation (e.g. treatment beliefs), instead of exploring a broad range of potential adherence determinants. The three inter-related studies reported in the subsequent chapters of this thesis seek to address these evidence gaps.

In Chapters 4, relevant demographic and treatment factors were explored using routinely collected objective adherence data among 126 adults in Sheffield over a 4-year period. This study found that age and the type of treatment regime (shorter term regimen for *P. aeruginosa* eradication vs longer term maintenance treatment) were associated with nebuliser adherence. There was a U-shape relationship between adherence and age, with lowest adherence among adults aged 19–25 years. Lower adherence was also noted for long-term nebuliser regimen (i.e. treatment duration >3 months) in comparison to shorter term regimen (typically used for *P. aeruginosa* eradication).

In Chapter 5, relevant psychological factors were explored using mixed methods design among 20 adults in Sheffield (10 high and 10 low adherers). This study has three main findings. First, both the qualitative and quantitative results indicate that high adherers were more likely to make nebuliser use habitual. Second, high adherers adapted more effectively to using nebulisers by creating and seizing opportunities for nebuliser use. Third, habit has the potential to attenuate perceived treatment burden among adults with CF.

In Chapter 6, replication for two of the three main findings from Chapter 5 (i.e. the habit-adherence association, and the potential of habit to attenuate perceived treatment burden) were attempted with a secondary analysis of the ACTiF pilot data. The ACTiF pilot, which recruited 64 participants from Nottingham and Southampton, is a two-centre external pilot trial to evaluate the feasibility of a full-scale nebuliser adherence intervention RCT. Analysis of ACTiF pilot data replicated the habit-adherence association observed in Chapter 5. However, the moderating effect of habit on perceived treatment burden was not replicated, in part due to limitations with the ACTiF pilot data.

Another finding from the ACTiF pilot data is the trend of declining adherence over time – this is consistent with the finding of lower adherence for long-term nebuliser regimen in Chapter 4.

Taken together, the studies reported in Chapters 4–6 point towards the difficulty of sustaining adherence to long-term nebuliser treatments, especially among younger adults with CF; and also highlights the role of habit in maintaining adherence.

Chapter 7, Section 2: How the research work presented in this thesis relates to other research work undertaken as part of the PhD and other work by the wider research group

Understanding the determinants of nebuliser adherence among adults with CF is important to design effective interventions, but it is only one cog in the wheel to develop, evaluate and implement effective adherence interventions for adults with CF. There are at least three other steps involved in the development of an effective adherence intervention.

First, evidence for specific behaviour change techniques (BCT) to target relevant behaviour determinants [431, 432] should be reviewed. This would allow the appropriate BCTs to be selected and combined in an adherence intervention, especially since interventions with more than one BCT tended to be more potent.[433-435] This piece of work has been undertaken by the wider research team during the development and iteration of a complex adherence intervention for ACTiF pilot (ISRCTN13076797) and CFHH RCT (ISRCTN55504164).

Second, a method should be developed for personalising the use of the various BCTs for an individual, instead of delivering a generic intervention with a ‘one size fits all’ approach. There is evidence that targeted behaviour change interventions tended to be more potent.[436-439] Variation in adherence during an intervention period could be used to identify response and guide intervention delivery.[440, 441] Statistical process control (SPC) is a visual form of time series analysis based on the statistical methods introduced by Shewhart in the 1920’s to help understand variation of a process with time.[442] Thus, SPC could potentially be used to personalise the delivery of BCTs; but the type I and type II errors associated with different SPC strategies as applied to nebuliser adherence data need to be clarified. The use of different SPC strategies to detect changes in nebuliser adherence have been explored using the Sheffield dataset and ACTiF pilot data as part of the PhD research.

Third, there is a need to understand the level of adherence which is adequate to sustain lung health and the minimum amount of improvement in adherence required to improve health outcomes. In the context of developing an effective adherence intervention, this understanding is critical to agree an explicit adherence target that is beneficial and clinically relevant for adults with CF. There is evidence that “100% adherence” may not be necessary to achieve health benefits, for example using $\geq 80\%$ of prescribed anti-hypertensives is adequate to control blood pressure.[443]

To begin the journey towards understanding 'how much adherence is enough', some of the required background work include identifying important clinical characteristics that determine treatment requirements, developing an adherence measure which reflects effectiveness of medication use, developing a better understanding of health outcomes in CF, and systematically exploring the interplay between clinical characteristics, prescribed treatments, adherence and health outcomes. Preliminary exploration of these issues has been performed using the Sheffield dataset as part of the PhD research, with the aim of replicating the analyses using data from the CFHH RCT.

The next step after developing an adherence intervention is to evaluate the efficacy and effectiveness of the intervention. Having completed the ACTiF pilot, the wider research team is currently evaluating a complex adherence intervention in the CFHH RCT.

Although evaluation follows on from intervention development, the learning required to develop an effective adherence intervention rarely occurs in a linear fashion.[444, 445] An experimental design is typically used to evaluate adherence interventions. Such design, which yields the least ambiguous cause and effect conclusions, is also useful to generate further knowledge regarding behaviour determinants, impact of specific BCTs on behaviour determinants, and the relationships between adherence and health outcomes;[446, 447] especially if adherence is carefully defined, and key outcomes and adherence determinants are accurately measured. Secondary data analysis following a clinical trial of adherence intervention can yield further learning to guide the iteration of adherence interventions, before subjecting the iterated intervention to further evaluation cycles. Therefore, secondary analyses using data from CFHH RCT (ISRCTN55504164) have been planned to further refine the complex adherence intervention, and also to try answer the 'how much adherence is enough' question.

Even a robust evaluation study providing incontrovertible evidence that a behaviour change intervention is effective does not necessarily guarantee the successful implementation of that intervention. A case in point is the Diabetes Prevention Program which has yet to be translated into clinical practice,[448] despite a landmark trial published in 2002 demonstrating a reduced incidence of diabetes by 58% for the lifestyle-modification programme compared to usual care among at-risk population.[449] By re-positioning the healthcare delivery sector as a set of nimble organisations focusing on on-going system improvement (i.e. as a 'learning health system' [450-453]), there is potential for quicker integration of an effective adherence intervention into routine clinical practice.[454] Therefore, the CFHH improvement collaborative (ISRCTN14464661) has been set up by the wider research team as a learning health system, in which adherence data are routinely and accurately collected via electronic data capture. The adherence data are used to inform on-going clinical practice, improve care over time with continuous learning and accelerate the integration of effective adherence interventions at the point of care.

Chapter 7, Section 3: Highlights and discussion points

Since this PhD was nested within a NIHR adherence programme grant, a national group of health services researchers was an immediate audience for outputs of the research. The findings of the PhD research have therefore influenced the design of the ACtiF pilot (ISRCTN13076797), CFHH RCT (ISRCTN55504164) and CFHH improvement collaborative (ISRCTN14464661). For example, the habit measure in these studies focused on habitual instigation, since the mixed methods study reported in Chapter 5 of the thesis found that effects of non-specific habit on nebuliser adherence may be more precisely attributed to instigation habit. The adherence metric used in these studies to reflect effective adherence is based on the method to quantify adherence [181, 182] that was developed as part of the PhD research. Likewise, the method to diagnose chronic *P. aeruginosa* infection in the CFHH RCT and CFHH improvement collaborative is based on a consensus definition [455] that was developed as part of the PhD research.

The studies presented in this thesis have also added to the current knowledge of factors associated with nebuliser adherence among adults with CF, especially in highlighting that nebuliser adherence among adults with CF is not just about “treatment burden”.

We often believe what we can sense. In the past, bacteria could not be seen but putrid odour could be smelt; hence the miasma theory (that noxious “bad air” is responsible for the spread of disease) was assumed to be true.[456] Currently, there is a temptation within the CF community to believe that “treatment burden” must be an insurmountable barrier to medication adherence because CF treatment regimens are complex and that complexity can be easily observed (e.g. as the number of medications to take or as time spent on treatments).

However, low adherence in CF is multi-factorial and more complex than it first seems. The literature review in Chapter 3 summarised a list of potential factors that may influence nebuliser adherence including age, gender, socioeconomic status, prescription factors, treatment burden, routine, disease severity, illness perception, disease / treatment knowledge, psychopathology, ways of coping, family relationship, relationship with the CF care team, other social relationship, self-efficacy and treatment beliefs. Over-coming one barrier may unearth another, hence simple strategies focusing only on one barrier to treatment have typically not achieved sustained improvement in adherence.

For example, treatment rationalisation (e.g. dropping inhaled mucolytic to “reduce treatment burden”) is often employed as a strategy to try improve adherence,[364] yet the few studies which looked at this strategy found no evidence of efficacy.[176] Treatment rationalisation might even be detrimental to health outcomes – the analysis in Chapter 4 found that treatment rationalisation was only associated with a modest increase in adherence by 4% to 8%, which probably represent less effective treatment (due to reduced target number of nebuliser doses to be taken) rather than more effective treatment (increase in the actual number of nebuliser doses taken). Other interventions

based solely on “reducing treatment burden” such as switching nebulised therapy to dry powder inhalers also did not demonstrate improvement in adherence beyond one year. More recent data showed similar adherence for nebulised therapy and dry powder inhalers.[219, 269]

Other forms of adherence intervention in CF include problem-solving to help people with CF overcome practical barriers to using nebuliser,[234, 236] whilst motivational interviewing [236] and providing education [234, 235] engaged reflective processes to change behaviour. Data in Chapters 4 & 6 show that sustaining long-term adherence is particularly challenging. There is also increasing recognition that effective means of initiating behaviour change may not necessarily sustain that change.[457] Yet the interventions used in previous CF studies lack a built-in mechanism to sustain improved adherence. Not surprisingly, the gains in adherence are often transient.[14, 15]

No study among people with CF has specifically investigated a habit-based behaviour change strategy to support nebuliser adherence or used habit strength to tailor intervention techniques. There is evidence in other long-term conditions to suggest that it may be more worthwhile for adherence interventions to target automatic processes such as habit. For example, a recent meta-analysis on 771 trials found medication adherence interventions that included habit formation were more effective than those that did not.[249]

Among people with CF, routinisation has been reported as a facilitator of nebuliser use.[251, 252, 259] Objective adherence data collected using electronic data capture have demonstrated that adolescents with CF are most adherent during school term-time weekdays.[171] This finding suggests that habit and routines (routine is more inherent during school term-time) may trump treatment burden (adolescents are likely to be busiest during school term-time, so should be most susceptible to lapse in adherence due to treatment burden) in regards to influencing adherence among people with CF. Both the studies in Chapters 5 & 6 add to the current evidence by demonstrating the association between habit and nebuliser adherence, and highlighting the potential for habit to moderate perceived treatment burden among adults with CF.

While evidence accumulates on the relevance of habit to nebuliser adherence, it is sufficiently clear that to change behaviour at the scale needed to improve the overall population health of people with CF, minds need to be changed about how to achieve this. The ineffectiveness of current adherence interventions for adults with CF should prompt the CF community to reflect on strategies to support adherence. Instead of merely focusing on treatment burden and reflective processes, habit formation among adults with CF warrants further investigations. Habit-formation advice could be part of a comprehensive and individualised package of intervention to support adherence, especially among people with low habit strength. Such advice – i.e. encouraging the use of treatments in specific and unchanging contexts, so that associations may develop between those contexts and treatment adherence – is simple to deliver.[314] In addition, habit strength should be assessed as an intervention outcome and habit formation might be prioritised as a goal for adherence interventions.

Chapter 7, Section 4: Future directions

The ineffectiveness of current adherence interventions for adults with CF is not just a call for action – it is also a call for better evidence. The studies presented in this thesis have identified three areas that requires further work, in order to generate more robust evidence for advancing the field of CF medication adherence.

The first area is the quality of research studies. Previous studies evaluating adherence determinants in CF have tended to find conflicting results, in part due to small sample sizes. Recruiting an adequate number of participants in a rare disease is challenging – despite the prolific increase in the number of CF clinical trials over the past three decades, quality of clinical trials (especially the sample size) has not improved.[458, 459] To achieve an adequate sample size which can provide more reliable findings, multi-centre (or even multi-national) studies would be needed. In a rare disease area, there is a particular need for the use of more efficient trial designs (especially efficient methods to recruit participants),[460-462] e.g. ‘master protocol’,[463] adaptive designs,[464] randomised registry trials,[465] and trials within cohort.[466] Since longer-term adherence is particularly problematic, studies with long term follow-up periods (e.g. more than two years) are also needed to understand the change in adherence over time.

The second area is taking a whole system perspective to investigate and improve CF medication adherence. The literature review in Chapter 3 showed that existing CF studies have only focused on understanding adherence of individual adults with CF and have not systematically included the entire cohort within a centre to understand adherence at a centre-level. Unlike most other long-term conditions whereby care are predominantly delivered by general practitioners in the community, healthcare for people with CF are delivered almost exclusively by multi-disciplinary teams through specialist CF centres.[124] The CF community is tight knit with cohesiveness enhanced by national CF Trusts / Foundations, which are patient and clinician advocacy organisations that support equity and quality of care with structures such as national CF registries. This cohesiveness provides a platform for system-wide learning and quality improvement.[467] As stated in Section 2.3, one of the key CF treatments is high calorie diet. The importance of aggressive nutritional support was not discovered via randomised controlled trials, but through comparisons of CF centres in Toronto and Boston back in the 1980’s.[468] Other quality improvement initiatives also have had profound impact on the lives of people with CF by transforming the delivery of healthcare.[467, 469, 470] Examples of successful quality improvement initiatives include reduced variation in screening rates for CF related diabetes, improved clinic attendances, streamlined approach to managing acute exacerbation, better infection control, seamless transition process and increased prescription of efficacious preventative inhaled therapies.[145, 374, 471-474] Although low levels of medication adherence and the potential health benefits from improved adherence should represent a low-hanging fruit to further improve CF clinical care, a large scale systematic quality improvement initiative around medication

adherence has not yet been published. The continuous quality improvement techniques e.g. benchmarking and the use of small tests of change (plan-do-study-act, PDSA) which have been so effective in transforming other aspects of CF care could also be harnessed to improve adherence at a centre level and drive quality improvement using adherence as a quality indicator. Therefore, there is also a need to better understand CF adherence from the whole system perspective.

The third area is the challenge of measuring psychological constructs and behaviour. Measuring psychological constructs that cannot be directly observed is especially challenging. None of the existing habit measures can fully capture the construct of habit as “a process by which a stimulus automatically generates an impulse towards enacting a behaviour”.[250] Striving for a “perfect” measure of habit is aspirational, but perhaps it is more pragmatic to develop a suite of habit measures that are adequate to provide insight even if that insight cannot be perfect. In terms of perceived treatment burden, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) treatment burden domain is limited by a lack of internal consistency, as highlighted by the analysis in Chapter 6 and also in other studies.[395, 428] To better understand perceived treatment burden among people with CF, a robust and comprehensive CF-specific treatment burden scale should be developed by taking into account the ‘taxonomy of treatment burden’ framework.[475-477]

Since CF is a multi-system disorder which necessitates multiple treatment modalities, it is imperative to understand whether increasing adherence to a specific treatment modality has the unintended consequence of reducing adherence to another treatment modality. Progress is being made in terms of objectively measuring adherence to other CF-related treatments. For example, physiotherapy adjuncts for airway clearance have been chipped (similar to an intelligent nebuliser device) to measure both adherence and quality of airway clearance techniques.[478, 479] Oral medications (e.g. pancreatic enzyme replacement therapy) can be monitored indirectly using intelligent pill bottles that can track the date and time of each bottle opening (e.g. the Medication Event Monitoring System, MEMS),[167] or directly using ingestible event marker which can detect if medication was actually ingested (e.g. Abilify MyCite, which is aripiprazole with an embedded sensor).[480] More self-monitoring devices are likely to be commercially available with advances in technology. However, further work is needed to embed these devices within routine clinical practice so that overall adherence to CF treatments can be better understood.

Further work is also required to enhance the adherence metric which was designed to reflect effectiveness of treatment regimen. A consensus exercise involving a broad group of CF clinicians could potentially identify other relevant factors that influence treatment effectiveness and methods considered acceptable for processing adherence data. A broad engagement in a consensus process would improve the acceptability of the adherence metric and make it more likely for the metric to be universally adopted. In addition, seeking the opinions of people with CF and their relatives / carers are important, since being fed back lower than expected levels of adherence might be perceived negatively and thus discourage engagement.[481] The think aloud method

[482] could be applied to systematically explore the views of people with CF and their relatives / carers. Different adherence metrics should also be empirically tested in a suitably large dataset with objective adherence data and carefully measured key outcomes. This will allow different data processing methods to be tested and help identify the optimum method of processing adherence data that most accurately reflect effective adherence.

Chapter 7, Section 5: Concluding remarks

The improvement in CF survival from less than 6 months in 1940's to 45–50 years in the 2010's is a testament to the increasing availability of efficacious treatment options and advances in care quality. Few other long-term conditions can match such improvements and advances. Yet not all the expected rewards from increasingly efficacious treatment options have been realised because treatment adherence in CF is generally suboptimal.

This thesis has provided an in-depth analysis of a broad range of clinical and psychological adherence determinants among adults with CF. Some of the new insights provided by this thesis may stimulate future research, in particular the potential for habit to moderate perceived treatment burden among adults with CF. A natural next step would be to extend my current research by using larger datasets from CFHH RCT and CFHH improvement collaborative for replication of findings and further analyses to better understand medication adherence among adults with CF.

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